Effects of Adenosine Compounds on Renal Function and Renin Secretion in Dogs

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ABSTRACT

In anesthetized salt-depleted dogs, infusion of adenosine (20 to 500 \( \mu \)g/min) directly into a renal artery induced an initial decrease of renal blood flow for 1 to 2 minutes but did not change or slightly increased this flow during the steady state. Statistically significant decreases occurred in glomerular filtration rate, filtration fraction, sodium excretion, and renal venous renin activity. Calculated afferent arteriolar resistance increased and efferent resistance decreased. 5'-AMP (50 to 200 \( \mu \)g/min) induced changes which were smaller but qualitatively similar to those of adenosine. ATP (50 to 500 \( \mu \)g/min) induced no initial reduction in blood flow, and, during the steady state, caused a significant increase in blood flow and decreases in glomerular filtration rate, filtration fraction, sodium excretion, and renal venous renin. Efferent resistance decreased but afferent resistance did not change. Cyclic AMP (1 to 5 \( \mu \)g/min) caused a very small initial transient reduction in blood flow but induced changes similar to those of ATP during the steady state. Inosine (200 \( \mu \)g/min) and inosine-5'-monophosphate (50 to 200 \( \mu \)g/min) produced no detectable effects. It is suggested that adenosine or 5'-AMP may be normal mediators of both autoregulation and renin secretion.

ADDITIONAL KEY WORDS

adenine nucleotides efferent dilation renal autoregulation sodium excretion

Several investigators (1-5) have demonstrated that intra-arterially administered adenosine and 5'-AMP increase renal vascular resistance, whereas ATP decreases it. However, most of these studies were performed using single injections, while steady-state data are required to evaluate the possible roles of these agents as intrarenal mediators (2, 6). Moreover, little is known about their effects on glomerular filtration rate, sodium excretion, and renin secretion, data which are needed to evaluate their sites of action. Our experiments were designed to study changes in these variables during continuous infusion of these agents directly into a renal artery.

Methods

Twenty-two male mongrel dogs weighing 25 to 34 kg were given mercuhydrin (80 mg im) 4 or 5 days before the experiments and thereafter were maintained on a diet containing 10 mEq Na/day (prescription diet h/d, Hill Packing Co.). All animals were anesthetized with sodium pentobarbital, 30 mg/kg iv, with supplements given as required. Via flank incisions, the left kidney was excised and the right ureter was catheterized with a polyethylene tube. To obtain renal venous blood, a polyethylene catheter (2.4 mm o.d.) was introduced into a femoral vein, passed up the inferior vena cava, and manipulated into the right renal vein; its position was verified at the end of the experiment. An electromagnetic flow probe was placed on the right renal artery, and the renal blood flow was continuously recorded by a square-wave electromagnetic flowmeter (Carolina). Care was taken not to cut or injure the visible nerve fibers around the renal artery. A 22-gauge needle attached to a polyethylene catheter was inserted directly into the renal artery proximal to the flow probe and was left in place throughout the experiment, and isotonic saline was infused continuously at the rate of 0.2 ml/min with or without the test drugs. A priming dose of creatinine was given, followed by continuous intravenous infusion at a rate of 0.2 ml/min for the measurement of glomerular filtration rate.
Filtration rate. Clearance periods were 8 to 12 minutes, and arterial and renal venous blood was collected in the middle of each period. Renin activity was assayed in renal venous plasma. Mean arterial blood pressure was monitored from a carotid artery catheter with a Statham transducer and Grass polygraph. All red cells collected were suspended in an equal volume of 6% dextran solution in isotonic saline and were returned to the dog through an external jugular vein catheter.

At least 45 minutes were allowed after completion of all surgical procedures and administration of the creatinine priming dose. After control clearances, an agent dissolved in saline was infused at a constant dose through the renal artery catheter for 20 minutes and further clearances were performed. After stopping the agent, clearances were performed 15 to 25 minutes later. This protocol was then repeated more than an hour after completion of the previous infusion, using a different dose. The agents infused were adenosine (5 to 500 µg/min), adenosine-5'-monophosphate-2H3 hydrate (5'-AMP; 20 to 200 µg/min), adenosine-5'-triphosphate disodium (ATP; 50 to 500 µg/min), adenosine-3',5'-cyclic phosphate monohydrate (cyclic AMP; 0.2 to 5 mU/min), inosine (200 µg/min), and inosine-5'-monophosphate disodium-7 H2O (IMP; 50 to 500 µg/min).

Plasma renin activity was analyzed by the method described previously (7), and was expressed as nanograms of angiotensin equivalents per milliliter of plasma. Addition of standard renin to plasma samples (10~3 unit of lyophilized renin2 per ml plasma) obtained before and during adenosine infusion caused the formation of identical amounts of pressor substance, thus demonstrating that the relationship between renin activity and renin concentration was not altered by adenosine. Hematocrit was measured by microcapillary tube. Renal plasma flow was obtained as renal blood flow times (1 — hematocrit). Methods for measurements of sodium and creatinine have been described previously (7). Statistical significance was evaluated by analysis of paired samples.

Results

Adenosine.—At the onset of infusion, blood flow showed an immediate transient reduction (mean decrease, 29%; range, 5 to 72%), but recovered toward control within 1 to 2 minutes. Data during the steady state were divided into three dose groups and are summarized in Table 1. The infusion of 200 to 500 µg/min, the largest dose, increased renal plasma flow slightly but significantly, but lower doses caused no significant change. Both glomerular filtration rate and filtration fraction were decreased significantly in the two higher dose groups. Sodium excretion also decreased markedly in all experiments of these two groups; the decrease was statistically significant only with the dose of 20 to 100 µg/min, because with 200 to 500 µg/min there was great variation in the magnitude of the changes between animals. Urine flow decreased almost in parallel with sodium excretion. Systemic blood pressure showed significant but very small decreases. The infusion of 5 µg/min produced no significant changes in renal function, except for a very small decrease in urine flow.

In most dogs, when the infusion of adenosine was stopped, there was a rapid transient increase of renal blood flow, generally of smaller magnitude than the transient decrease at the onset of infusion. Within 5 minutes, renal blood flow returned toward preinfusion control values, although when 200 to 500 µg/min was given it remained slightly higher than its control value. As shown in Table 1, glomerular filtration rate, filtration fraction, and mean arterial blood pressure all returned to their preinfusion control values. Sodium excretion and urine flow tended to increase above their control values.

The effects of adenosine on renal venous renin are shown in Table 1 and Figure 1. In the two higher dose groups, adenosine decreased renin in every experiment except one with 20 to 100 µg/min; when this experiment, in which renin increased progressively, was excluded, the decrease in renin was also statistically significant for the group (P < 0.05), as well as for the group given 200 to 500 µg/min. There was no significant difference between the magnitude of the renin decreases for the two groups. The infusion of 5 µg/min produced no changes in renin. When the infusion was stopped, renin general.

1Agents were obtained from Calbiochem, Los Angeles, California, except ATP from Sigma Chemical, St. Louis, Mo.
2Nutritional Biochemicals, Cleveland, Ohio.
### Summary of Effects of Adenosine and ATP Infusions on Renal Function and Renal Venous Renin

<table>
<thead>
<tr>
<th>Summary of Effects of Adenosine and ATP Infusions on Renal Function and Renal Venous Renin</th>
<th>RPF (ml/kg/min)</th>
<th>GFR (ml/kg/min)</th>
<th>Filtration fraction</th>
<th>Urine flow (ml/kg/min)</th>
<th>Na excretion (mmol/kg/min)</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Renal venous renin (ng/ml/mln)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine, 800 to 2000 μg/min (7)</td>
<td>7.55 ± .70</td>
<td>3.05 ± .15</td>
<td>.02 ± .03</td>
<td>15.5 ± 2.0</td>
<td>.92 ± .42</td>
<td>144.0 ± 7.4</td>
<td>19.7 ± 2.5</td>
</tr>
<tr>
<td>(I - C)</td>
<td>.07 = .27†</td>
<td>.07 = .19‡</td>
<td>.13 ± .04 †</td>
<td>.30 ± 1.8</td>
<td>.60 ± .34</td>
<td>-8.0 ± 1.2 †</td>
<td>-9.8 ± 2.1 †</td>
</tr>
<tr>
<td>(R - C)</td>
<td>.07 = .14*</td>
<td>.02 = .14</td>
<td>.03 ± .03</td>
<td>5.6 ± .8‡</td>
<td>.07 ± .33</td>
<td>-8.0 ± 1.0</td>
<td>7.7 ± 3.1*</td>
</tr>
<tr>
<td>Adenosine, 80 to 100 μg/min (7)</td>
<td>8.49 ± .74</td>
<td>2.56 ± .21</td>
<td>.31 ± .03</td>
<td>17.1 ± 2.5</td>
<td>1.42 ± .41</td>
<td>180.0 ± 2.5</td>
<td>26.3 ± 8.7</td>
</tr>
<tr>
<td>(I - C)</td>
<td>.12 ± .21</td>
<td>.08 ± .23</td>
<td>.10 ± .02 †</td>
<td>-4.8 ± 1.6 *</td>
<td>-82 ± 33*</td>
<td>-3.6 ± 1.1 †</td>
<td>-11.3 ± 4.8</td>
</tr>
<tr>
<td>(R - C)</td>
<td>.04 ± .10</td>
<td>.19 ± .02</td>
<td>.03 ± .02 †</td>
<td>5.1 ± 2.5</td>
<td>.05 ± .28</td>
<td>-2.6 ± 2.2</td>
<td>10.3 ± 7.2</td>
</tr>
<tr>
<td>Adenosine, 5 μg/min (4)</td>
<td>9.88 ± .75</td>
<td>2.20 ± .25</td>
<td>.23 ± .05</td>
<td>12.6 ± 1.9</td>
<td>.50 ± .16</td>
<td>130.0 ± 6.8</td>
<td>26.4 ± 8.3</td>
</tr>
<tr>
<td>(I - C)</td>
<td>.08 ± .71</td>
<td>.08 ± .08</td>
<td>.01 ± .02</td>
<td>-1.0 ± 2.1</td>
<td>-8.0 ± .07</td>
<td>-4.0 ± 2.0</td>
<td>-2.6 ± 2.2</td>
</tr>
<tr>
<td>(R - C)</td>
<td>.16 ± .73</td>
<td>.22 ± .04</td>
<td>.01 ± .05</td>
<td>-1.0 ± 1.5</td>
<td>-6.0 ± .05</td>
<td>-6.0 ± 3.0</td>
<td>2.5 ± 1.8</td>
</tr>
<tr>
<td>ATP, 50 to 500 μg/min (7)</td>
<td>7.09 ± .60</td>
<td>2.09 ± .19</td>
<td>.31 ± .03</td>
<td>18.3 ± 4.9</td>
<td>1.31 ± .49</td>
<td>131.3 ± 3.3</td>
<td>28.6 ± 4.2</td>
</tr>
<tr>
<td>(I - C)</td>
<td>1.25 ± .44*</td>
<td>.05 ± .07 †</td>
<td>.00 ± .02 †</td>
<td>1.6 ± 1.1</td>
<td>-28 ± 21</td>
<td>-3.1 ± 1.8</td>
<td>-10.3 ± 2.4</td>
</tr>
<tr>
<td>(R - C)</td>
<td>.07 ± .14</td>
<td>.06 ± .08</td>
<td>.01 ± .01</td>
<td>2.1 ± .08</td>
<td>.15 ± .40</td>
<td>3 ± 2.2</td>
<td>10.5 ± 6.5</td>
</tr>
</tbody>
</table>

C = control; Δ (I - C) = difference between infusion and control; Δ (R - C) = difference between recovery and control; RPF = renal plasma flow; GFR = glomerular filtration rate. Number in parentheses is number of experiments.

Values are means ± se. Statistical significance when evaluated by paired analysis; *P < .05; †P < .01; ‡P < .05; §P < .001.
Effect of adenine on renal venous renin activity.

Effect of 5'-AMP, ATP, and cyclic AMP on renal venous renin activity.

ly increased above its preinfusion control value in the two higher dose groups, but the change was significant only with 200 to 500 µg/min.
ADENOSINE COMPOUNDS, RENAL FUNCTION, RENIN

Table 2

Effects of 5'-AMP Infusion on Renal Function in Eight Experiments

<table>
<thead>
<tr>
<th></th>
<th>BPF (ml/kg/min)</th>
<th>GFR (ml/kg/min)</th>
<th>Urine flow (ml/kg/min)</th>
<th>Na excretion (mmol/l)</th>
<th>Mean arterial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>8.77</td>
<td>-2.96</td>
<td>16.3</td>
<td>1.16</td>
<td>137</td>
</tr>
<tr>
<td>Δ (I - C)</td>
<td>1.91</td>
<td>-1.62</td>
<td>-8.8</td>
<td>-84</td>
<td>-1</td>
</tr>
<tr>
<td>Δ (R - C)</td>
<td>1.07</td>
<td>8.8</td>
<td>15.1</td>
<td>15.3</td>
<td>3</td>
</tr>
<tr>
<td>C</td>
<td>7.02</td>
<td>1.83</td>
<td>11.0</td>
<td>13.3</td>
<td>123</td>
</tr>
<tr>
<td>Δ (I - C)</td>
<td>1.59</td>
<td>-2.21</td>
<td>1</td>
<td>-5.3</td>
<td>-8</td>
</tr>
<tr>
<td>Δ (R - C)</td>
<td>0.5</td>
<td>6.5</td>
<td>11.1</td>
<td>-5.3</td>
<td>-8</td>
</tr>
<tr>
<td>C</td>
<td>9.45</td>
<td>4.57</td>
<td>24.3</td>
<td>.94</td>
<td>114</td>
</tr>
<tr>
<td>Δ (I - C)</td>
<td>-1.56</td>
<td>-6.4</td>
<td>-8.3</td>
<td>-4.3</td>
<td>1</td>
</tr>
<tr>
<td>Δ (R - C)</td>
<td>-1.24</td>
<td>-9.4</td>
<td>-2.0</td>
<td>-3.9</td>
<td>1</td>
</tr>
</tbody>
</table>

50 μg/min

| C      | 9.63            | 2.58            | 12.3                   | .85                  | 142                           |
| Δ (I - C) | 1.01           | -4.7            | -3.3                   | -3.9                 | -4                            |
| Δ (R - C) | .04            | 5.1             | 5.1                    | .57                  | -2                            |
| C      | 6.17            | 1.76            | 11.1                   | 1.16                 | 153                           |
| Δ (I - C) | .21            | -3.9            | -1.3                   | -3.8                 | -9                            |
| Δ (R - C) | -0.5           | 2.4             | 2.4                    | 3.1                  | -1                            |
| C      | 9.52            | 2.34            | 18.5                   | .38                  | 119                           |
| Δ (I - C) | -.79           | 1.1             | -1.2                   | -.01                 | -1                            |
| Δ (R - C) | -.85           | 27              | 8.2                    | .35                  | -3                            |

100 μg/min

| C      | 8.86            | 2.67            | 10.2                   | .16                  | 157                           |
| Δ (I - C) | 1.88           | .09             | 0                      | -.01                 | -1                            |
| Δ (R - C) | 1.24           | 9.7             | 9.7                    | -.24                 | -9                            |
| C      | 10.67           | 2.47            | 8.8                    | .29                  | 128                           |
| Δ (I - C) | 0              | -.17            | .7                     | .06                  | 0                             |
| Δ (R - C) | -.43           | 22              | 2.7                    | .20                  | 1                             |

Abbreviations as in Table 1.

5'-AMP...The infusion of 5'-AMP also produced an immediate transient reduction in renal blood flow, but of lesser magnitude (mean decrease, 14%; range, 6 to 27%) than that produced by adenosine. Data for each experiment during steady-state infusion are shown in Table 2 and Figure 2. Statistical analyses were not done for each dose group because of the small numbers of animals. Renal plasma flow showed no consistent change at any dose. Glomerular filtration rate and filtration fraction decreased during all infusions of 200 μg/min, but showed no consistent changes with lower doses. Large decreases in sodium excretion occurred in all experiments with 200 μg/min and in two of three with 50 μg/min. When data of all experiments were analyzed together, the decrease in sodium excretion was statistically significant (P<0.05). As shown in Figure 2, renal venous renin decreased during infusion of 5'-AMP in all experiments except one; the change for all experiments analyzed together was statistically significant (P<0.02). As with adenosine, cessation of the infusion was associated with a transient increase in renal blood flow, followed by a return to control values; glomerular filtration rate, filtration fraction, and renal venous renin all returned to their preinfusion control values, and sodium excretion tended to increase above control value.
ATP.—There was no initial reduction of renal blood flow at the onset of ATP infusion; during the steady state (Table 1), renal plasma flow increased significantly. Glomerular filtration rate and filtration fraction were significantly decreased. Sodium excretion was decreased in six of seven experiments, though the change for all experiments analyzed together was not significant. Renal venous renin decreased in six of seven experiments (Fig. 2), and the change was significant (P < 0.01). After cessation of infusion, all the above variables returned to preinfusion control values.

Cyclic AMP.—The infusion of 1 to 5 mg/min cyclic AMP induced an immediate transient reduction in renal blood flow of smaller magnitude (mean decrease, 8%; range, 4 to 12%) than that produced by adenosine and 5'-AMP; this was not observed with smaller doses, 50 to 200 /μg/min. Table 3 and Figure 2 summarize data for each experiment during steady-state infusion. Renal plasma flow increased in seven of eight experiments, and glomerular filtration rate and filtration fraction decreased in all; when data of all experiments were analyzed together, the changes in renal plasma flow, glomerular filtration rate, and filtration fraction were statistically significant (P < 0.05, < 0.05, and < 0.02, respectively). Sodium excretion de-
Increased in four of five experiments with 1 to 5 mg/min, but showed no consistent changes with lower doses. Systemic blood pressure decreased in all experiments except one with 50 μg/min; the decrease were largest with 5 mg/min. The change in blood pressure for all experiments analyzed together was statistically significant (P<0.01). Large decreases of renal venous renin occurred during both experiments with 5 mg/min and in two of three with 1 mg/min (Fig. 2). No consistent change was observed during infusions of 50 to 200 μg/min. As with adenosine and 5'-AMP, there were transient, though much smaller, decreases in renal blood flow after stopping the infusion, and these were followed by a return to control values; all of the above variables tended to return to their preinfusion control values after cessation of infusion.

**Discussion**

**Renal Hemodynamics**—In contrast to the report of Thurau (2), these studies indicate that the steady-state effects of adenosine and 5'-AMP differ from those observed during single injections of these agents, since total renal resistance was either unchanged or, in the case of 200 to 500 μg/min adenosine, decreased. Moreover, their effects are quite complex, as evidenced by the large decreases in glomerular filtration rate in the absence of similar changes in renal blood flow. To analyze these effects, we calculated afferent and efferent arteriolar resistances (Table 5), using methods described in the appendix. Adenosine (20 to 500 μg/min) increased afferent resistance and decreased efferent resistance, both changes being statistically significant. In doses of 200 μg/min, 5'-AMP induced resistance changes similar to those of adenosine. However, the changes for all experiments analyzed together were not statistically significant because lower doses had no consistent effect on either resistance. Thus 5'-AMP seems to act in a manner similar to that of adenosine, but is less effective, possibly because adenosine passes through cell mem-
TABLE 5
Percent Changes of Afferent and Efferent Arteriolar Resistances during Infusion of Adenosine Compounds Compared to Control Periods

<table>
<thead>
<tr>
<th>Compound</th>
<th>Afferent Arteriolar Resistance</th>
<th>Efferent Arteriolar Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine (30-500 μg/mln)</td>
<td>+20.2 ± 6.5 (16)</td>
<td>-31.1 ± 7.8 (16)</td>
</tr>
<tr>
<td>5'-AMP (30-500 μg/mln)</td>
<td>+9.8 ± 11.9</td>
<td>-19.2 ± 8.4</td>
</tr>
<tr>
<td>ATP (5-500 μg/mln)</td>
<td>-0.8 ± 3.6</td>
<td>-28.9 ± 4.3</td>
</tr>
<tr>
<td>Cyclic AMP (5-500 μg/mln)</td>
<td>-3.9 ± 3.6</td>
<td>-12.7 ± 3.3</td>
</tr>
</tbody>
</table>

P < .01, NS = not significant. Number in parentheses is number of experiments.

branes more easily than 5'-AMP (8). Although adenine nucleotides are rapidly hydrolyzed to adenosine in blood (9), it is unlikely that enough degradation of 5'-AMP to adenosine could have occurred between the sites of injection and response to account for the effects observed during infusion of 5'-AMP. Finally, these hemodynamic effects were not caused by adenosine breakdown products, since neither inosine nor IMP induced any observable changes.

The afferent constriction induced by adenosine and 5'-AMP is probably due to a direct effect on the arteriolar smooth muscle, but the decrease in efferent resistance could be caused in various ways. First, when afferent constriction occurs, filtration fraction decreases, resulting in a decreased hematocrit of efferent arteriolar blood and, thereby, reduced efferent resistance. However, the average decrease in efferent hematocrit was calculated to be only 4% during infusion, using the formula described in the appendix. With a control hematocrit of 48%, as in our experiments, the decrease of 4% in efferent hematocrit would cause a reduction in efferent resistance of only about 12% (10), which is far below the observed decrease of 30% for adenosine. Second, afferent constriction might induce a myogenically mediated efferent dilation. Finally, decreased renin secretion or a direct dilator effect could contribute. Our data do not permit these factors to be separated.

The effect of ATP is less complex, since decreased efferent resistance was the sole finding (Table 5), confirming the previous report of Harvey (1). Since no afferent constriction occurred, the primary cause of decreased efferent resistance is probably either decreased renin secretion or a direct dilator effect.

These observations are not compatible with the hypothesis (3) that ATP might be a chemical mediator of renal autoregulation, since, if it were released in response to decreased perfusion pressure, its efferent dilation effect would restore blood flow but decrease glomerular filtration rate even more. On the other hand, adenosine or 5'-AMP could constitute one of the autoregulatory mechanisms, if the lowered efferent resistance caused by these agents were totally due to reduced efferent hematocrit and myogenically dilated secondary to afferent constriction.

Namely, if they were released by high perfusion pressure, they would constrict afferent arteries so as to keep the changes of both renal blood flow and glomerular filtration rate very small, under these conditions, the secondary decrease in efferent resistance would be minimal. Although changes have been reported in renal nucleotide metabolism during complete renal ischemia (11), there are presently no data concerning the rates of adenosine and 5'-AMP generation during changes in renal perfusion pressure over the autoregulatory range. However, the direct relationship between glomerular filtration rate, sodium reabsorption rate, and renal oxygen consumption which exists for the kidney (12-14), suggests that increased renal perfusion pressure might indeed induce in-
ADENOSINE COMPOUNDS, RENAL FUNCTION, RENIN

• Adenosine 20-500 μg/min
• 5'-AMP 50-200 μg/min
• ATP 50-500 μg/mln
• Cyclic AMP 1-5 mg/min

\[ y = 0.84x - 15.7 \]
\[ r = 0.527 \]
\[ F = 0.01 \]

Changes in glomerular filtration rate (CFR) and sodium excretion during infusion of adenosine compounds. Data for all low dose experiments with each agent are not included because of the absence of changes.

Changes in generation of these metabolites. It should be emphasized, however, that the relevance of our experiments to autoregulation may be tenuous, since they were performed in only one special circumstance—the salt-depleted state. Additional experiments with different doses in a variety of situations will be required.

Cyclic AMP, even in very large doses, caused smaller changes in renal function than the other adenosine compounds. It is questionable at present whether exogenous cyclic AMP can enter cells at a rate sufficient to raise

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9 Adenosine generation by kidney has not yet been proven, since it is controversial whether 5'-AMP is catabolized to inosine via adenosine (15) or IMP (11).

intracellular concentration (16), because of low penetration through cell membranes and fast conversion to 5'-AMP by phosphodiesterase (17, 18). Because such large amounts of cyclic AMP were required, the transient reduction in renal blood flow at the onset of infusion might be due to an effect induced by 5'-AMP (or adenosine) which had been formed by degradation of cyclic AMP. However, in the steady state cyclic AMP caused resistance changes similar to those by ATP rather than those by adenosine or 5'-AMP (Table 5), i.e., decreased efferent resistance without change in afferent resistance.

Sodium Excretion.—Figure 3 demonstrates the highly significant correlation between changes in glomerular filtration rate and sodium excretion for all adenosine compounds infused. It is most likely that the decreases in sodium excretion produced by these agents are completely ascribable to decreases in glomerular filtration rate.

Renin Secretion.—The values reported in this study are all renal venous renin activities rather than total renin secretory rates. However, they may be used as indicators of changes in secretory rates, since the blood flow changes alone were too small to account for the decreases in renal venous renin activities. Renin secretion was decreased by all of the adenosine compounds studied (but not by inosine and IMP) despite frequent simultaneous decreases in sodium excretion and afferent arteriolar pressure. Therefore, this inhibition of renin release is opposite to the change predicted by previously postulated baroreceptor (19) and macula densa (20) theories. Moreover, the effect on renin could be dissociated from any consistent changes in sodium excretion and renal hemodynamics, since inhibition was observed in association with efferent dilation alone (ATP and cyclic AMP), with afferent constriction and efferent dilation (adenosine and high doses of 5'-AMP), with no detectable resistance changes (lower doses of 5'-AMP), with decreased sodium excretion (adenosine, ATP, and high doses of 5'-AMP and cyclic AMP), and with no consistent changes in sodium excretion (lower doses of 5'-AMP). Accordingly, this inhibition of renin release may be due to a direct inhibitory effect of adenosine compounds on the juxtaglomerular apparatus, although possible changes in distribution of intrarenal blood flow must also be considered.

As described above for autoregulation, if adenosine or 5'-AMP generation were increased during elevation of renal perfusion pressure and other situations associated with decreased renin secretion, these agents might be the normal mediators controlling renin secretion. A recent study (21) showing that saline loading decreases ATP and increases 5'-AMP in kidney tissue of dogs is consistent with this hypothesis, since renin secretion is suppressed in saline-loaded animals. It should be noted that Thurau (2) has also postulated that ATP metabolites might control renin release, but he hypothesized that they would stimulate renin release, which was not confirmed by our data. Finally, Winer and colleagues (22) reported that, in normal dogs, adenosine, 5'-AMP and ATP did not change renal venous renin. However, as their study was performed in dogs having low control renins, it is likely that a further decrease in renin could not occur or could not be detected.

In the present experiments, renin secretion was either inhibited or unchanged by cyclic AMP. This is in contrast to the findings of Winer et al. (22) and Michelakis et al. (23) that cyclic AMP stimulated renin release in vivo and in vitro, respectively. Winer and co-workers observed stimulation with the same doses that produced no effect in the present experiments; this discrepancy might be due to the fact that renin activity was already high in our dogs because of salt depletion and further increases of the very small magnitude reported by them might not have been manifest. The inhibition of renin secretion in our experiments occurred only with much higher doses of cyclic AMP than those used by Winer and co-workers (22).

Appendix

Afferent and efferent arteriolar resistances \( (R_a, R_e) \) were calculated as follows, assuming...
ADENOSINE COMPOUNDS, RENAL FUNCTION, RENIN

peritubular capillary pressure to be 15 mm Hg, regardless of arterial pressure (24-26):

\[
R_e = \frac{MAP - P_g}{RBF} \quad \text{and} \quad R_e = \frac{P_g - 15}{BBF - GFR}
\]

where \( P_g \) is glomerular capillary pressure. Note that the equation for \( R_e \) assumes a constant peritubular capillary pressure; any error introduced in the present calculation by this assumption would, however, be small, since both control peritubular capillary pressure and its expected changes are small compared to glomerular capillary pressure.

\( P_g \) during control periods was assumed to be 85 mm Hg (27), and \( P_g \) during infusion periods was obtained from the following formulas:

\[
P_g = \frac{(CQ_P - (COP_g + 15) GFR)}{\frac{(1 - \text{filtration fraction} + 22)}{2}}
\]

where \( COP_g \) is mean glomerular colloid osmotic pressure, and superscripts \( C \) and \( I \) refer to the values during control and infusion periods, respectively.

Hematocrit of efferent arteriolar blood \( (H_t) \) was calculated:

\[
H_t = Ht \times \frac{RBF}{BBF - GFR}
\]

where \( Ht \) is hematocrit of arterial blood.

References

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TAGAWA, VANDER


Effects of Adenosine Compounds on Renal Function and Renin Secretion in Dogs
HITOSHI TAGAWA and ARTHUR J. VANDER

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