Natriuretic and Hypotensive Effect of Adenosine-1 Blockade in Essential Hypertension

Marjolijn van Buren, Joost A. Bijlsma, Peter Boer, Herman J.M. van Rijn, Hein A. Koomans

We studied the effects of a single dose (100 mg orally) and repeated administration (100 mg o.d. for 7 days) of FK453, a novel adenosine-1 receptor antagonist, on renal sodium handling and blood pressure in eight patients with essential hypertension. Within 60 minutes after administration of FK453, sodium excretion increased threefold. This occurred in the absence of a change in renal hemodynamics, assessed from inulin and para-aminohippurate clearance, and was accompanied by increased fractional excretion of lithium, phosphate, and uric acid and by increased excretion of calcium and magnesium. Maximal free water clearance data showed an increase in maximal urine flow and distal delivery term and a decrease in the diluting segment reabsorption term. FK453 also decreased blood pressure and increased heart rate, but this did not occur until about 3 hours after ingestion, that is, when the natriuresis was already over. The natriuretic effect of FK453 was short-lasting, and continued use of FK453 was in fact accompanied by some net sodium retention. Blood pressure on the seventh day before FK453 treatment was not different from blood pressure before administration of the first dose of FK453. Again an acute natriuretic response followed, although less than after the first dose. Changes in intrarenal sodium handling parameters, blood pressure, and heart rate were similar to those seen after the first dose. The natriuretic and hypotensive effects of FK453 indicate that adenosine-1 receptor activity plays a role in the regulation of blood pressure and renal sodium handling in patients with essential hypertension. Although these findings are not necessarily specific for this condition, it seems worthwhile to evaluate whether adenosine-1 antagonism can be used as a mode to treat hypertension. (Hypertension. 1993;22:728-734.)

Key Words • adenosine • renal sodium handling • blood pressure • hypertension, essential

A denosine is a nucleoside present in nearly all human tissues. There appear to be at least two different subtypes of adenosine cell surface receptors, which are known as A1- and A2-receptors. Selective stimulation of these receptor subtypes yields opposite effects, and the regional effect of adenosine therefore depends on the distribution of these receptor subtypes. When infused systemically, adenosine lowers blood pressure, since A2-receptor-mediated vasodilation prevails over A1-receptor-mediated vasoconstriction. In the kidney, however, adenosine causes net vasoconstriction, since A1-receptor-mediated constriction of the afferent arterioles prevails over the A2-receptor-mediated vasodilation. Several studies have shown that adenosine, whether infused intravenously, into the aorta, or into the renal artery, causes sodium and water retention. Inversely, intrarenal infusion of a nonspecific adenosine blocker has been shown to stimulate sodium excretion. In the isolated perfused rat kidney model, it was found that adenosine's action to cause sodium retention was bound to A1-receptor stimulation, whereas A2-receptor stimulation stimulated the excretion of sodium.

Very little is known about the role of endogenous adenosine in the regulation of blood pressure and sodium balance. Also, it is unknown whether adenosine plays a role in the pathogenesis of human essential hypertension. If it does, a relative increase in A1-receptor stimulation rather than A2-receptor stimulation would be suspected from the above findings. Accordingly, selective A1-receptor blockade might be an appropriate mode to treat hypertension. Until now, these issues could not be studied since selective antagonists for the study in humans were not available. Clearly, application of nonselective adenosine blockade with drugs such as theophylline would not be appropriate since the effects of A1-receptor blockade might be offset by the unavoidable A2-receptor blockade. The recent development of FK453, a pyrazolopyridine derivative, characterized as a highly selective A1-receptor antagonist available for oral administration in humans, provides us with a tool to start studying the above issues. In this first study in patients with essential hypertension, we analyzed the effects on blood pressure, renal hemodynamics and sodium handling, and sodium balance of FK453 (100 mg) given once daily for a period of 7 days.

Methods

The effects of orally administered FK453 were studied in eight patients (four men and four women) with mild to moderate essential hypertension, after informed consent had been obtained. The study was approved by the University Hospital Ethical Committee for Studies in Humans.

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Patients

The age range of the patients was 27 to 62 years (mean, 47.4±3.8 years). The mean duration of hypertension was 10 years (range, 1 to 30 years). Patients who had a recent history of angina pectoris or cerebrovascular accident and patients with clinically significant ventricular impairment or conduction abnormalities were excluded from the study. Also, all patients with other systemic disease were excluded.

Study Protocol

Antihypertensive medication was stopped at least 3 weeks before the study commenced. The patients were instructed to use a diet containing about 150 mmol sodium and 80 mmol potassium daily. Twenty-four-hour sodium excretion was assessed on the 14th day, seventh day, and the final 3 days before treatment with FK453.

On the first day of treatment, FK453 (100 mg) was given in the middle of a clearance study and during automatic blood pressure and heart rate recording (see below) to evaluate the acute effects of FK453 on renal function and blood pressure. Afterward, FK453 was taken daily at 10 AM, and 24-hour urine collections were continued. On the seventh day of FK453 treatment, clearance experiments and blood pressure measurements were again performed, and the seventh day dosage of FK453 was taken in the middle, similar to the protocol on day 1.

Lithium carbonate (50 mg) was taken orally at 10 PM on the eve of the clearance studies, and the patients refrained from food until after the clearance study. No xanthine-containing drinks were allowed from 12 hours before until 24 hours after each clearance study. Clearance studies were performed under conditions of maximal water diuresis, with the subjects in a supine position. Antecubital veins were catheterized to allow blood sampling and to (contralaterally) infuse a solution containing 25 mg/mL inulin and 25 mg/mL para-aminohippuric acid (PAH) to measure glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), respectively. After a priming dose, this solution was infused at a rate of 0.005 mL/kg per minute throughout the clearance experiment. Maximal water diuresis was induced by administration of a water load of 25 mL/kg body weight and was maintained by drinking amounts of water matching urinary output. After 1 hour of equilibration, the actual clearance study was started. Urine collections were made every 30 minutes, and plasma samples were drawn at the midpoint of each urine collection period. After four baseline collections, FK453 (100 mg) was administered orally, and the clearance study was continued for another 4-hour collection period. Blood and urine samples were analyzed for clearance calculations (see below). In addition, blood samples were taken for assessment of plasma renin activity (PRA) and aldosterone 1 hour before FK453 administration (P2) and in the second hour thereafter (P8). Urinary cyclic adenosine monophosphate (cAMP) was measured in samples 2, 4, 6, and 8.

After the end of the clearance study, an additional urine collection was made for 2 hours, and the subjects remained supine for another 4 hours. Throughout the clearance study and this 4-hour supine period, blood pressure and heart rate were monitored every 15 minutes with an automated sphygmomanometer device (Omega 1000, Invivo Research Laboratories, Tulsa, Okla).

Laboratory Techniques

Each blood and urine sample was analyzed for sodium and potassium (Autocoll 743 flame photometer, Instrumentation Laboratories, Lexington, Mass), chloride, phosphate, uric acid, magnesium, and calcium (Technicon RA-1000 autoanalyzer, Tarrytown, NY), and osmolality (Advanced Osmometer). Lithium was hydrolyzed to fructose and determined photometrically with indolacetic acid, and PAH was determined photometrically by a chromogenic aldehyde reaction. Urinary cAMP was determined by radioimmunoassay. PRA and plasma aldosterone were determined by standard radioimmunoassay.

Calculations and Statistical Analysis

Values are given as mean±SEM. PRA and aldosterone were analyzed after logarithmic transformation. Statistical analysis was performed using analysis of variance of randomized block design. The treatment variance ratios indicate whether a variable overall is significantly altered by FK453 administration. The interaction variance ratio indicates whether significant changes between the responses on day 1 and day 7 were present. If these variance ratios reached statistical significance, the differences between the means were analyzed at 5% and 1% significance levels by the Least Significant Difference test.

Clearances were calculated according to standard formulas. Free water clearance ($C_{H_2O}$) during maximal water diuresis was taken as an index of sodium reabsorption in the diluting segment, that is, distal to the point of isotonicity in the medullary thick ascending limb of Henle’s loop. Changes in $C_{H_2O}$ augmented by chloride clearance, written as the equation

$$[(C_{H_2O}+C_{Cl})/C_{main}]$$

FIG 1. Bar graphs show urinary sodium excretion (UNaV) before and after administration of FK453 on day 1 (left) and on day 7 (right). Arrow indicates the administration of FK453. The first eight columns denote half-hour collections, and the final column denotes a 2-hour collection. *P<.01, compared with baseline levels before FK453 administration.
TABLE 1. Electrolyte Excretions

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 h After FK453</th>
<th>2 h After FK453</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNaV, µmol/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>200.6±36.9</td>
<td></td>
<td>410.5±66.9*</td>
<td>662.4±88.5*</td>
</tr>
<tr>
<td>Day 7</td>
<td>156.9±27.6</td>
<td></td>
<td>225.8±33.3</td>
<td>400.5±65.5*</td>
</tr>
<tr>
<td>UKV, µmol/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>77.8±12.5</td>
<td></td>
<td>83.7±7.6</td>
<td>102.9±10.5*</td>
</tr>
<tr>
<td>Day 7</td>
<td>81.0±10.0</td>
<td></td>
<td>60.4±7.7</td>
<td>71.7±9.4</td>
</tr>
<tr>
<td>FE Na, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>1.4±0.2</td>
<td></td>
<td>2.9±0.6*</td>
<td>3.9±0.5*</td>
</tr>
<tr>
<td>Day 7</td>
<td>1.2±0.2</td>
<td></td>
<td>1.8±0.3†</td>
<td>2.7±0.5*</td>
</tr>
<tr>
<td>FE K, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>17.8±1.6</td>
<td></td>
<td>19.7±1.5</td>
<td>21.6±1.1*</td>
</tr>
<tr>
<td>Day 7</td>
<td>15.7±1.6</td>
<td></td>
<td>16.5±1.9</td>
<td>17.7±1.6†</td>
</tr>
<tr>
<td>FE Li, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>32.7±2.4</td>
<td></td>
<td>38.2±4.3†</td>
<td>39.5±2.4*</td>
</tr>
<tr>
<td>Day 7</td>
<td>30.8±2.3</td>
<td></td>
<td>35.9±2.5†</td>
<td>41.5±3.7*</td>
</tr>
<tr>
<td>FE Mg, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>10.7±1.2</td>
<td></td>
<td>12.2±1.6*</td>
<td>13.4±1.2*</td>
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<tr>
<td>Day 7</td>
<td>10.1±1.3</td>
<td></td>
<td>11.4±1.7†</td>
<td>12.8±1.4*</td>
</tr>
<tr>
<td>FE Ca, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>14.4±3.0</td>
<td></td>
<td>16.5±1.7</td>
<td>20.5±2.7*</td>
</tr>
<tr>
<td>Day 7</td>
<td>17.6±1.8</td>
<td></td>
<td>20.6±1.7†</td>
<td>24.5±1.5*</td>
</tr>
<tr>
<td>UMgV, µmol/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3.3±0.4</td>
<td></td>
<td>5.1±0.6†</td>
<td>7.5±0.8*</td>
</tr>
<tr>
<td>Day 7</td>
<td>2.8±0.4</td>
<td></td>
<td>3.7±0.4</td>
<td>6.7±1.2*</td>
</tr>
<tr>
<td>UCaV, µmol/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3.6±0.6</td>
<td></td>
<td>6.8±1.3*</td>
<td>9.9±1.3*</td>
</tr>
<tr>
<td>Day 7</td>
<td>3.5±0.6</td>
<td></td>
<td>4.9±0.8*</td>
<td>7.6±0.6*</td>
</tr>
</tbody>
</table>

UNaV indicates urinary sodium excretion; UKV, urinary potassium excretion; FE Na, fractional sodium excretion; FE K, fractional potassium excretion; FE Li, fractional lithium excretion; UMgV, urinary magnesium excretion; and UCaV, urinary calcium excretion. Baseline measurement indicates the mean of the last two 30-minute collections before FK453 administration; 1 h after FK453, mean of first two 30-minute collections after FK453 administration; 2 h after FK453, mean of third and fourth 30-minute collection periods after FK453 administration.

*P<.01, †P<.05, compared with corresponding baseline value. Column A indicates whether the response on day 7 differs from the response on day 1.

were taken as an index of changes in fractional solute delivery to the diluting segment and changes in the equation

\[
\frac{C_{\text{H}_{2}O}(C_{\text{H}_{2}O}+C_{\text{CO}})}
\]

as an index of changes in diluting segment reabsorption. The relevance of these equations has been discussed elsewhere.14

Results

Baseline Values Before FK453

Sodium excretion on the final 3 days of the washout period averaged 117±15, 147±25, and 121±24 mmol/24 h, respectively. Mean potassium excretion in this period was 73±7, 69±7, and 66±3 mmol/24 h, respectively; urinary creatinine excretion was 13.1±1.3, 13.3±1.7, and 13.0±1.5 mmol/24 h, respectively. Body weight decreased slightly in the washout period from 85.5±4.0 to 84.5±4.1 kg (P<.05). Average blood pressure values at the end of the washout period were 167±6 mm Hg (systolic blood pressure) and 108±2 mm Hg (diastolic blood pressure).

Effects of First Dose of FK453

Ingestion of 100 mg of FK453 was quickly followed by a threefold increase in urinary sodium excretion, already visible in the second 30-minute period after administration (Fig 1). Apparently, this effect was short-lasting, since average sodium excretion during the 2 hours after the clearance experiment approached baseline values.

The effects of FK453 on renal hemodynamics and sodium handling parameters are listed in Table 1 and Table 2. For the purpose of this presentation, the
There was some tendency for GFR to increase in the 30-minute data have been pooled into hourly averages.

Effects of Continued Administration of FK453

On the first day of FK453 administration urinary sodium excretion tended to be higher compared with that in the washout period, but this difference was not significant (Fig 3). During the next 3 days, sodium retention was observed despite continued use of FK453. There was no net effect on potassium excretion. Despite the sodium retention, body weight decreased significantly from 84.5±4.1 kg before the first dose of FK453 to 83.5±4.0 kg before the last dose of FK453 on day 7 (P<.01), and baseline PRA was significantly higher on day 7 compared with day 1 (Table 3).

When given on the seventh consecutive day, FK453 was again followed by an acute increase in sodium excretion (P<.01) (Fig 1), although significantly less than observed after the first dosage (P<.01). Again no change was found in renal hemodynamics, and the effects on renal sodium handling parameters and electrolyte excretion were comparable to those found after the first dose of FK453 (Tables 1 and 2) except that no change occurred in potassium excretion.

Blood pressure and heart rate before the last dose of FK453 on day 7 were fully comparable to the baseline values before the first dose of FK453. Again, a fall in blood pressure did not occur until 2 hours after the ingestion of FK453 and was accompanied by an increase in heart rate (Fig 2). These changes brought about by FK453 were fully comparable to those seen after the first dose of FK453.

PRA, the baseline value of which was already somewhat elevated, increased further after FK453, but again no significant increase in plasma aldosterone was found. Urinary cAMP excretion showed a similar response to that seen after the first dose of FK453.

Discussion

We evaluated the effects of acute and 7-day treatment with FK453, a novel highly selective adenosine A1-receptor antagonist, on renal hemodynamics, sodium handling, and blood pressure in patients with essential hypertension. The effects of FK453 appeared to consist of a fast effect of diuresis and natriuresis without concomitant changes in renal hemodynamics and a slower systemic hemodynamic effect resulting in a decrease in blood pressure and an increase in heart rate.

The specificity of FK453 to act as an A1-receptor antagonist has been demonstrated directly in rats. FK453 appeared to be at least 300 times more selective for the A1-receptor than for the A2-receptor and, at infusion rates as low as 1 μg/kg per minute, inhibited...
the bradycardiac effect of the specific \( A_2 \)-receptor agonist N-cyclopentyladenosine. Direct data in humans that FK453 is a selective \( A_2 \)-receptor antagonist are not yet available. Indirect support in the present data in humans is provided by the increase in PRA and urine cAMP. Indeed, stimulation of \( A_1 \)-receptors inhibits the production of cAMP in various kidney cells and suppresses renin release, whereas \( A_2 \)-receptor stimulation has the opposite effect.

As mentioned, studies in the isolated perfused rat kidney suggest that it is through the \( A_1 \)-receptor that adenosine causes renal sodium retention since \( A_1 \)-receptor stimulation decreases sodium excretion, whereas \( A_2 \)-receptor stimulation does the opposite. In contrast to this idea, it has been found in rats that systemic infusion of a specific \( A_2 \)-receptor agonist caused sodium retention to the same extent as did infusion of adenosine or a specific \( A_1 \)-receptor agonist. However, since in that study each infusion was followed by a large fall in blood pressure, indirect mediation of these effects cannot be excluded. The present data in humans are in agreement with the idea that the sodium-retaining effect of adenosine is an \( A_1 \)-receptor–mediated effect since specific \( A_1 \)-receptor blockade with FK453 was followed by sodium excretion.

Since \( A_1 \)-receptor stimulation is related to afferent arteriolar vasoconstriction, vasodilation might be expected to occur after FK453 administration. However, FK453 had no significant effect on renal hemodynamics, except for some tendency for GFR and ERPF to increase at the end of our clearance study. Obviously, we cannot exclude that such changes would become significant at some later stage. In this respect, it may be important that systemic hemodynamic changes also did not occur until after the clearance experiment. In any case, the increase in sodium excretion occurred sooner in the absence of changes in renal hemodynamics. This observation is in concert with the recent finding in dogs that intrarenal infusion of a nonspecific adenosine blocker also stimulated sodium excretion in the absence of a change in renal hemodynamics. Apparently, these effects of adenosine blockade concern a direct interaction with tubular reabsorption.

The present study, also designed to analyze the effects of FK453 on renal electrolyte handling, showed that these effects were complex. FK453 caused an increase in maximal urine flow, uric acid and phosphate clearance, and the quotient \([C_{\text{Na}}+C_{\text{Cl}}]/C_{\text{Na}}\); each of these changes was compatible with suppression of solute reabsorption in the proximal tubules. Lithium clearance, although not a perfect marker of proximal tubule reabsorption, increased so substantially that suppression of proximal tubule reabsorption indeed seems likely. At the same time, FK453 increased minimal urine osmolality.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>2 h After FK453</th>
<th>Baseline</th>
<th>2 h After FK453</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA, fmol/L per second</td>
<td>194±39</td>
<td>376±94*</td>
<td>318±60</td>
<td>486±98*</td>
</tr>
<tr>
<td>Plasma aldosterone, pmol/L</td>
<td>300±31</td>
<td>444±95</td>
<td>365±45</td>
<td>421±62</td>
</tr>
<tr>
<td>U(cAMP)V, nmol/min</td>
<td>1.7±0.4</td>
<td>2.2±0.4†</td>
<td>1.4±0.4</td>
<td>2.0±0.4†</td>
</tr>
</tbody>
</table>

PRA indicates plasma renin activity; and U(cAMP)V, urinary cyclic AMP excretion.

*P<.01, †P<.05, compared with corresponding baseline value.
and decreased diluting segment reabsorption estimated from the term \([C_{\text{H}_2O}/(C_{\text{Na}}+C_{\text{Cl}})]\). During maximal water diuresis, this segment comprises Henle’s loop from the halfway point of the medullary ascending limb, the distal tubule, and the collecting tubule.13,14 The large increase in magnesium excretion suggests that suppressed reabsorption in Henle’s loop was at least partly responsible for this fall in diluting segment reabsorption.23 These changes would imply that the tubular effects of FK453 include increased delivery to the macula densa, which should lead to a decrease in GFR through the tubuloglomerular feedback mechanism. This did not occur, and we have to assume that FK453 inhibited this response, which is in agreement with the notion that A₁-receptors mediate this response.24,25

We recently studied the effects of theophylline, a nonspecific adenosine antagonist, on renal function in normotensive subjects.27 The effects on renal sodium handling were very similar to those found in the present study after FK453 administration, except that GFR and filtration fraction increased. This difference may be due to the additional A₁-receptor blockade by theophylline, causing efferent vasoconstriction.2,20 Alternatively, the difference may be a matter of drug dosage or may be related to different responses in normotensive and hypertensive individuals. The marked similarity of the changes in intrarenal sodium handling observed after FK453 and theophylline suggests that control of intrarenal sodium handling by adenosine is mainly through the A₁-receptor.

Direct data obtained in animal experiments regarding the effect of adenosine on intrarenal sodium handling is scanty. In fact, it is difficult to explain the present findings from those data. Micropuncture studies in rats showed no effect of adenosine on late proximal tubule volume delivery of superficial nephrons.8 Adenosine blockade with theophylline suppressed water reabsorption in Henle’s loop but without a significant change in chloride reabsorption.28 A₁-receptors are probably present in afferent arterioles,29 glomeruli,30 medullary and cortical thick ascending limb,31 medullary and medullary collecting duct.15,33 Recently, A₁-receptors have also been identified on the proximal tubule.34 However, we have no information about the effect of stimulation of these receptors on net reabsorption.

Ingestion of FK453 was followed by a substantial decrease in blood pressure, which began after about 3 hours and lasted at least 3 hours. This observation is in line with the fact that A₁-receptor stimulation causes vasoconstriction2,2,3,4 and suggests that, at least in essential hypertension, A₁-receptor stimulation contributes to the peripheral arterial tone. Associated with the fall in blood pressure was an increase in heart rate. Although a physiological link to the decrease in blood pressure seems obvious, a direct effect of FK453 is also likely since A₁-receptor stimulation inhibits the sinoatrial node activity.35 Indeed, the heart rate increase was relatively large and, especially after the first dose of FK453, occurred relatively early (Fig 2).

Pharmacokinetic studies showed peak plasma concentrations of FK453 between 2 and 3 hours and a halflife of 1.5 hours after a single oral dose of FK453 in healthy humans (personal communication, J. Rose, Guy’s Drug Research Unit, London, UK), which would predict short-lasting effects. The natriuretic effect of FK453 was indeed limited to the first hours after ingestion. The decline in blood pressure, although it is unclear why this started later than the natriuretic response, may have contributed to the fact that the natriuretic effect was aborted relatively early. Despite continued use of FK453, the sodium balance changed into net sodium retention during the days after the first dose. Since these data were not obtained under strictly controlled conditions, they have to be interpreted with some reserve. However, it is possible that repeated blood pressure drops by the daily use of FK453 caused this initial sodium retention, overruling the short natriuretic effect of the drug. Indeed, the finding that on the seventh day FK453 was still followed by an acute increase in sodium excretion accompanied by changes in renal sodium handling parameters similar to those observed after the first ingestion of the drug suggests a short natriuretic action of the drug. The effects on blood pressure and heart rate also did not last throughout a day since the (predrug) values on day 7 did not differ from those on day 1.

It is interesting to compare our results in hypertensive patients with those obtained in normotensive subjects. Balakrishnan et al36 demonstrated that in healthy subjects, sodium excretion had increased approximately fourfold in the second hour after a single oral dose of FK453 (100 mg) and declined in the third hour. This effect is quite comparable to the natriuretic response observed in the hypertensive patients in our study. However, in contrast to our findings, no changes in blood pressure or heart rate were observed in these normotensive subjects.36 The reason for this discrepancy is not apparent. At this moment it seems too early to suggest that altered control of A₁-receptor activity contributes to the genesis of essential hypertension.

From the present data, we conclude that adenosine A₁-receptor antagonists may indeed prove to be effective antihypertensive agents. The combination of natriuretic action with undisturbed GFR, peripheral vasodilation, uricosuric action, and absence of potassium loss composes a potentially beneficial drug profile. Studies with adjusted dose regimens may reveal whether longer lasting antihypertensive effects can be obtained. Such
studies will also reveal whether the tachycardiac response to \( A_1 \)-receptor blockers poses a problem that precludes their use as monotherapy. It is also clear that subpopulations may be specifically responsive to \( A_1 \)-receptor blockade, and whether additional measures such as diet improve sensitivity to these drugs.

**Acknowledgments**

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