Prevention of Radiocontrast-Induced Nephropathy by Adenosine Antagonists in Rats with Chronic Nitric Oxide Deficiency

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Abstract. To evaluate therapeutic options for the prevention of radiocontrast media (RCM)-induced nephropathy, a model was developed in which rats received N^6-nitro-L- arginine methyl ester (L-NAME) for 10 wk in order to inhibit nitric oxide (NO) synthetase. This study tests the hypothesis that infusion of an adenosine antagonist before RCM application may avoid the vasoconstrictive response in NO-depleted rats. Rats received L-NAME for 10 wk orally (50 mg/L drinking water) to achieve NO depletion. Renal function was determined by [3H]leucine clearance for analysis of the GFR and by flowmetry for assessing renal blood flow (RBF). After a control clearance period (baseline clearance period), the renal response to RCM application (sodium diatrizoate, 2 ml/kg body wt) was measured two times every 30 min starting 30 min after RCM application (clearance periods 1 and 2). L-NAME rats and control rats received two adenosine antagonists. The nonselective adenosine antagonist theophylline was given as an initial bolus of 50 µmol/kg body wt within 10 min, followed by continuous infusion of 100 µmol/kg body wt per h, and the specific adenosine A1-receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) was given as a bolus of 100 µg/kg body wt before RCM application. Results were compared with vehicle infusion.

In the control group, no significant change of GFR or RBF could be detected after application of RCM with or without prior infusion of DPCPX or theophylline. In L-NAME rats, RBF decreased significantly after RCM application (baseline, 5.6 ± 0.2 ml/min; first clearance period, 4.6 ± 0.3 ml/min [P < 0.05]; second clearance period, 4.3 ± 0.3 [P < 0.01]). GFR was also reduced in L-NAME rats without previous infusion of theophylline or DPCPX (baseline, 0.95 ± 0.1 ml/min; first clearance period, 0.83 ± 0.1 ml/min; second clearance period, 0.69 ± 0.1 ml/min [P = 0.058]). Prior treatment with either theophylline or DPCPX resulted in complete protection against a decline of RBF and GFR induced by RCM in L-NAME rats.

Rats with chronic NO blockade showed a significant increase of the renal vasoconstrictive effect of contrast media. Application of L-NAME in rats seems to constitute a suitable animal model to study the pathophysiology of radiocontrast media-induced nephropathy. In this animal model, administration of adenosine antagonists prevented the decline of GFR and RBF. (J Am Soc Nephrol 8: 1125–1132, 1997)

Administration of hyperosmolar contrast media has long been recognized to induce profound changes in renal hemodynamics and occasionally has led to acute renal failure in humans. In animals and humans, systemic administration of contrast media, as well as direct injection of contrast media into the renal artery, results in a short increase of renal blood flow (RBF) and a subsequent transient decrease of RBF and GFR (1–3). Although many attempts have been made to elucidate the mechanisms of these actions, the results, for the most part, have been inconclusive. One major obstacle in analyzing the mechanism of contrast media-induced changes in renal hemodynamics is the lack of an accepted animal model (3). Rat models of diseases that are believed to be related to contrast media-induced acute renal failure, e.g., in diabetes mellitus, seem to be unresponsive to contrast media application as far as the effects on GFR and RBF are concerned (4,5). Only severe renal injuries, such as bilateral renal artery occlusion (6,7), or additional application of other nephrotoxic agents, e.g., gentamycin, render reproducible results of radiocontrast media (RCM) nephrotoxicity in rats (8).

Renal vasoconstriction after RCM administration is induced mainly by an increase of the preglomerular arteriolar resistance and seems to be an important factor in radiocontrast media-induced nephropathy (RCIN) (9–12). Although a number of renal vasoactive agents such as angiotensin II or norepinephrine have been studied with respect to RCM-induced vasoconstriction (1,13,14), a convincing causative role has not been found for any of these factors. Recent studies indicated that nitric oxide (NO) plays a major role in RCIN (15,16). Therefore, we tested the hypothesis that chronic blockade of the NO synthetase may result in a higher susceptibility to the vasocon-
strictive effect of RCM. It has been shown that RCM increases urinary excretion of adenosine (17) and that RCIN can be attenuated with theophylline, which acts as an unspecific adenosine antagonist (17,18). Thus, we also studied the effects of a prior infusion of two adenosine antagonists (unspecific adenosine antagonist theophylline and the specific adenosine A1-receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine [DPCPX]) on RCM-induced vasoconstriction.

Materials and Methods

Male Munich Wistar rats were used after approval of the study protocol by the Institutional Board for Animal Use. All animals were given a standard rat chow (containing 0.9% calcium, 0.7% phosphorous, 0.2% magnesium, 0.2% sodium, and 1.0% potassium). Initial weight of the rats was 200 to 220 g. On the day before the experiment, food was withheld with free allowance of water.

Study Protocol

Male Munich Wistar rats without pharmacological pretreatment for 10 wk were assigned as controls. The rats were given regular tap water during the entire pre-experimental period, or N-omega N02-nitro-l-arginine methyl ester (L-NAME) was added to the drinking water (50 mg/ml, approximating an intake of about 5 mg/kg per d).

Animal Preparation. On the day of the experiment, the rats were anesthetized with thiopental (80 mg/kg, intraperitoneally) and placed on a heated servo-controlled table to maintain the body temperature at 37°C monitored by rectal thermometry. After tracheotomy, three polyethylene catheters were inserted in the right internal jugular vein for infusion of saline (0.85 g/dl), tritium-labeled inulin (1.33 μCi/h; DuPont, Bad Homburg, Germany), and drugs (theophylline, DPCPX, or saline plus vehicle). The total infusion rate was set at 5 ml/hr throughout the experiment. The right femoral artery was catheterized for blood sampling and continuous monitoring of arterial pressure (pressure transducer; Tokshier Electron, Tokyo, Japan). The left kidney was exposed by flank incision, and a flow probe connected with an electromagnetic flowmeter (Carolina Medical, King, NC) was fitted around the renal artery to measure RBF. Radioactivity in plasma and urine was measured in a liquid scintillation counter (Packard, Meridian, CT), and the GFR was calculated with standard formulas. Urine was collected via catheters placed in the left ureter.

Measurement of RBF and GFR. One control clearance period (clearance period 0; Figure 1) was performed to determine the initial rates of GFR and RBF. Each clearance period comprised a 30-min urine collection, with one blood sample taken at midpoint. After the control period (90 min after preparation), the contrast medium (sodium diatrizoate, Urografin®, Schering, Berlin, Germany) was given at a dose of 2 ml/kg body wt. The same preparation of sodium diatrizoate was used as in humans. The contrast medium was injected directly into the jugular vein over a period of 2 min. Subsequently, three more clearance periods were performed, each lasting 30 min (Figure 1).

Theophylline and DPCPX Administration. Theophylline, dissolved in 0.85 g/dl saline, was infused at a rate of 100 μmol/kg body wt per h starting after a bolus of 50 μmol/kg body wt given 60 min before contrast media application. DPCPX was given as one bolus of 100 μg/kg body wt dissolved in one milliliter of NaCl-DMSO solution (DMSO: NaCl = 1:6) 60 min before contrast media application. To evaluate further effects of L-NAME, 10 of the L-NAME rats received an intravenous bolus of L-NAME (1 μg/kg per min) before application of contrast media, which did not result in a further decrease of RBF or GFR. Figure 1 summarizes the study protocol.

Experimental Groups

Group 1 (Control + Vehicle). On the day of the experiment, rats received an intravenous bolus injection of NaCl-DMSO (DMSO: NaCl = 1:6) solution (1 ml serving as control for DPCPX) followed by 0.85% saline (serving as control for theophylline), followed by sodium diatrizoate after 60 min.

Group 2 (Control + Theophylline). Male Munich Wistar rats received drinking water (normal tap water as a control for L-NAME) for 10 wk (n = 8). On the day of the experiment, the rats were administered an intravenous bolus of NaCl-DMSO (DMSO:NaCl = 1:6) solution (1 ml serving as a control for DPCPX). Theophylline, dissolved in 0.85% saline, was infused at a rate of 100 μmol/kg body

![Figure 1. Study protocol.](image-url)
wt per h after a bolus of 50 μmol/kg body wt over the study period, followed by sodium diatrizoate after 60 min.

**Group 3 (Control + DPCPX).** Male Munich Wistar rats received drinking water (normal tap water as control for L-NAME) for 10 wk (n = 9). DPCPX was given as a bolus of 100 μg/kg body wt dissolved in 1 ml of NaCl-DMSO solution (DMSO:NaCl = 1:6), followed by 0.85% saline (serving as control for theophylline), followed by sodium diatrizoate after 60 min.

**Group 4 (L-NAME + Vehicle).** The rats received L-NAME (50 mg/L drinking water) for 10 wk (n = 9). On the day of the experiment, rats were administered an intravenous bolus of NaCl-DMSO (DMSO:NaCl = 1:6) solution (1 ml serving as control for DPCPX), followed by 0.85% saline (serving as control for theophylline), followed by sodium diatrizoate after 60 min.

**Group 5 (L-NAME + Theophylline).** The rats received L-NAME (50 mg/L drinking water) for 10 wk (n = 8). On the day of the experiment, the rats were administered an intravenous bolus of NaCl-DMSO (DMSO:NaCl = 1:6) solution (1 ml serving as control for DPCPX). Theophylline, dissolved in 0.85% saline, was infused at a rate of 100 μmol/kg body wt per h after a bolus of 50 μmol/kg body wt during the study period, followed by sodium diatrizoate after 60 min.

**Group 6 (L-NAME + DPCPX).** The rats received L-NAME (50 mg/L drinking water) for 10 wk (n = 10). DPCPX was given as a bolus of 100 μg/kg body wt dissolved in 1 ml of NaCl-DMSO solution (DMSO:NaCl = 1:6), followed by 0.85% saline (serving as control for theophylline), followed by sodium diatrizoate after 60 min.

**Statistical Analyses**

All data are expressed as mean ± SEM. Statistical analysis was performed using ANOVA and t-test for paired and unpaired data. A P value of <0.05 was considered significant.

**Results**

**Effect of L-NAME Pretreatment on Mean Arterial Pressure and Renal Hemodynamics at Baseline**

Mean arterial pressure (MAP) was elevated in the L-NAME groups (groups 4 through 6) shortly after preparation and remained slightly elevated in these groups during the entire study period. The differences were statistically significant at the beginning of the experiment only (Figure 2). Concerning renal hemodynamics, GFR and RBF did not differ at baseline between control rats (groups 1 through 3) and L-NAME-treated rats (groups 4 through 6). Renal vascular resistance was significantly elevated in the L-NAME groups (Table 1). Ten additional rats received an intravenous bolus of L-NAME (1 μg/kg per min) before application of contrast media, which did not result in a further decrease in RBF or GFR.

**Effect of L-NAME Pretreatment on MAP and Renal Hemodynamics after Contrast Media Application**

After contrast media application, MAP was slightly reduced in all groups of rats without reaching statistical significance. GFR remained constant during the experiment in group 1 (Table 1, Figure 3). In L-NAME-pretreated rats (group 4), GFR declined constantly over the entire study period, but this decline did not reach significance with P = 0.058 (Table 1, Figure 3). RBF also remained constant over the entire study period in group 1 (Table 1, Figure 4). In L-NAME-pretreated rats (group 4), RBF decreased significantly after RCM application (Table 1, Figure 4). When calculating the percentage of intraindividual change, a significant decrease of GFR and RBF was seen in L-NAME rats (Figure 5).

![Figure 2](image_url)

*Figure 2.* Changes in mean arterial pressure (MAP) during the study period. Differences between L-NAME groups and control groups were significant at baseline (P < 0.05). After preparation, the decrease in MAP was significant for all groups. Initially, theophylline (groups 2 and 5) induced a significant increase of MAP. At the end of the experiment, there was a decrease of MAP (*P < 0.05 compared with values before theophylline administration). Group 1, control + vehicle; group 2, control + theophylline; group 3, control + DPCPX; group 4, L-NAME + vehicle; group 5, L-NAME + theophylline; group 6, L-NAME + DPCPX.
Table 1. Renal hemodynamics*

<table>
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<tr>
<th>Group/Treatment</th>
<th>n</th>
<th>Body Weight (g)</th>
<th>Period</th>
<th>GFR (ml/min)</th>
<th>RBF (ml/min)</th>
<th>FF</th>
<th>RVR (mmHg·min·ml⁻¹)</th>
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<tr>
<td>Group 1</td>
<td>10</td>
<td>327 ± 4</td>
<td>0</td>
<td>0.92 ± 0.09</td>
<td>5.79 ± 0.17</td>
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<td>16.3 ± 0.5</td>
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<td>1</td>
<td>0.89 ± 0.13</td>
<td>5.87 ± 0.18</td>
<td>0.31 ± 0.05</td>
<td>15.5 ± 0.9</td>
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<td></td>
<td></td>
<td></td>
<td>2</td>
<td>0.94 ± 0.13</td>
<td>5.62 ± 0.18</td>
<td>0.34 ± 0.05</td>
<td>15.7 ± 1.0</td>
</tr>
<tr>
<td>Group 2</td>
<td>8</td>
<td>320 ± 8</td>
<td>0</td>
<td>1.33 ± 0.08b</td>
<td>5.74 ± 0.13</td>
<td>0.46 ± 0.02</td>
<td>18.5 ± 0.7</td>
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<tr>
<td>control + theophylline</td>
<td></td>
<td></td>
<td>1</td>
<td>1.27 ± 0.17</td>
<td>5.51 ± 0.11</td>
<td>0.47 ± 0.07</td>
<td>16.7 ± 0.8</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1.14 ± 0.08</td>
<td>5.65 ± 0.11</td>
<td>0.41 ± 0.03</td>
<td>15.8 ± 0.9</td>
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<tr>
<td>Group 3</td>
<td>9</td>
<td>350 ± 7</td>
<td>0</td>
<td>1.14 ± 0.06</td>
<td>5.29 ± 0.18</td>
<td>0.41 ± 0.02</td>
<td>14.8 ± 0.5</td>
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<tr>
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<td>1.28 ± 0.08</td>
<td>5.59 ± 0.33</td>
<td>0.44 ± 0.04</td>
<td>13.5 ± 0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1.25 ± 0.06</td>
<td>5.76 ± 0.33</td>
<td>0.41 ± 0.03</td>
<td>13.0 ± 0.5</td>
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<tr>
<td>Group 4</td>
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<td>0.95 ± 0.12</td>
<td>5.56 ± 0.17</td>
<td>0.33 ± 0.04</td>
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<tr>
<td>l-NAME + vehicle</td>
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<td>0.83 ± 0.13</td>
<td>4.57 ± 0.25c,d</td>
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<td>22.0 ± 1.5c</td>
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<td>0.69 ± 0.13</td>
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<td>0.33 ± 0.06</td>
<td>23.2 ± 2.0c</td>
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<td>Group 5</td>
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<td>5.69 ± 0.19</td>
<td>0.40 ± 0.08</td>
<td>22.1 ± 1.0c</td>
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<td>l-NAME + theophylline</td>
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<td>1.21 ± 0.20</td>
<td>5.76 ± 0.21</td>
<td>0.47 ± 0.08</td>
<td>22.9 ± 1.3c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1.01 ± 0.18</td>
<td>5.79 ± 0.21</td>
<td>0.37 ± 0.06</td>
<td>20.0 ± 1.0c</td>
</tr>
<tr>
<td>Group 6</td>
<td>10</td>
<td>396 ± 9</td>
<td>0</td>
<td>0.95 ± 0.14</td>
<td>5.95 ± 0.06</td>
<td>0.32 ± 0.05</td>
<td>21.1 ± 0.7c</td>
</tr>
<tr>
<td>l-NAME + DPCPX</td>
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<td>1</td>
<td>1.04 ± 0.16</td>
<td>5.58 ± 0.25</td>
<td>0.37 ± 0.06</td>
<td>21.6 ± 1.2c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1.00 ± 0.14</td>
<td>5.46 ± 0.25</td>
<td>0.37 ± 0.05</td>
<td>21.8 ± 1.0c</td>
</tr>
</tbody>
</table>

* RBF, renal blood flow; FF, filtration factor; RVR, renal vascular resistance; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; l-NAME, N⁵-nitro-L-arginine methyl.

b P < 0.001 compared with group 1.
c P < 0.05 compared with rats without l-NAME pretreatment.
d P < 0.05 compared with baseline period.
* P < 0.01 compared with baseline period.

Figure 3. Changes in GFR after application of contrast media. group 1, control + vehicle; group 2, control + theophylline; group 3, control + DPCPX; group 4, l-NAME + vehicle; group 5, l-NAME + theophylline; group 6, l-NAME + DPCPX.

Effect of Theophylline and DPCPX Pretreatment on MAP, GFR, and RBF at Baseline

MAP was significantly increased by theophylline treatment (groups 2 and 5) and decreased significantly until the end of the experiment (Figure 2). DPCPX-treated rats (groups 3 and 6) showed a slow, but not significant, decline in MAP over the study period (Figure 2). Theophylline-treated rats (groups 2 and 5) showed an elevated GFR at baseline (Table 1), which reached statistical significance in rats without l-NAME (group 2) pretreatment (P < 0.001 compared with group 1). Baseline
values for RBF did not differ between the groups with theophylline pretreatment and the vehicle groups in rats with L-NAME pretreatment as well as in controls. DPCPX-treated rats (groups 3 and 6) did not show a significant difference in GFR at baseline (Table 1) compared with control rats with and without L-NAME pretreatment (groups 1 and 4). Baseline values for RBF did not differ between the groups with theophylline pretreatment and the vehicle groups in rats with L-NAME pretreatment and in controls. DPCPX-treated rats (groups 3 and 6) showed elevated levels of RBF in the case of L-NAME pretreatment (group 6).

**Effect of Theophylline DPCPX Pretreatment on MAP, GFR, and RBF after Contrast Media Application**

After contrast media application, MAP was significantly lowered in theophylline-treated rats (groups 2 and 5). GFR and RBF remained constant during the entire study in animals after theophylline infusion before RCM application in control rats and in L-NAME rats (Table 1, Figures 3 and 4). The same was true for application of DPCPX before RCM. When calculating the percentage of change at the end of the study and at baseline, no significant change could be demonstrated for rats pretreated with DPCPX or theophylline.

**Discussion**

In animals and humans, systemic administration of contrast media, as well as direct injection into the renal artery, result in a short increase of RBF and a subsequent transient decrease of RBF and GFR (1,2). Rat models of diseases that are believed to be related to contrast media-induced acute renal failure, e.g., in diabetes mellitus, seem to be unresponsive to contrast media application as far as the effects on GFR and RBF are concerned (3,4). Even uninephrectomy does not potentiate contrast media nephrotoxicity in streptozotocin-induced diabetic rats (5). Only severe renal injuries, such as bilateral renal artery occlusion (6,7), uninephrectomy combined with severe salt depletion (10), or additional application of other nephrotoxic agents, e.g., gentamycin or indomethacin, render reproducible results of contrast media nephrotoxicity in rats (8,19).

Because it was suggested that RCIN develops as a result of a deficiency of vasodilatory metabolites (9,16) including PGI2 and endothelium-derived relaxing factor (NO), we hypothesized that chronic inhibition of NO synthetase might render the kidney susceptible to RCM, as has been shown recently for a short intravenous injection of L-NAME (16). Injection of sodium diatrizoate resulted in a marked decrease in RBF in hypertensive (L-NAME) rats in this study (Figure 4). The absolute values of GFR also declined constantly over the entire study period, but this decline did not reach significance (Table 1, Figure 3). When calculating the percentage of intraindividual change in each rat, we also demonstrated a significant decline of RBF and GFR in L-NAME rats (Figure 5). This supports previous observations that rats under NO blockade are more sensitive to the hemodynamic changes induced by contrast media (16). GFR at baseline was not diminished in our L-NAME rats. The reason for this could be the dosage of L-NAME that we chose. The L-NAME dose in this study (approximately 5 mg/kg per d for 10 wk) was rather low compared with other reports, which demonstrated a decline in GFR with a dose of 25 mg/kg per d given over 6 wk (20). On the other hand, we observed a significant increase in renal vascular resistance in all animals treated with L-NAME (Table 1), indicating a vasoconstrictive action of L-NAME. These hemodynamic changes seem to sensitize the rats to other vasoconstrictive effects like those induced by radiocontrast media. We cannot rule out that higher doses of L-NAME might be able to induce a greater decline in GFR or RBF after radiocontrast media application. Interestingly, administration of L-NAME (1 µg/kg per min) immediately before contrast media application, which we performed in 10 animals, did not result
in a further decrease in RBF or GFR. This indicates that the maximum of vasoconstriction based on the NO system has already been reached by oral L-NAME application. The decline in GFR under chronic L-NAME administration observed with higher L-NAME doses (20) may be related to structural changes induced by high blood pressure itself. This assumption is further supported by studies using antihypertensive drugs in this rat model (20,21).

The advantages of an animal model that uses chronic L-NAME treatment seems to be simplicity and the fact that except for L-NAME, no other nephrotoxic agents or surgical maneuvers are needed to induce RCIN. The decrease in RBF obtained after contrast media administration in animals pretreated with L-NAME was approximately 25% after 90 min, which is within the same range obtained with other animal models of RCIN (10,15,22,23). Short infusion of L-NAME followed by an infusion of isothalamate has also been shown to result in a 50% decrease in cortical and outer medullary blood flow and a subsequent decrease in GFR (16). When one views the profile of patients at risk for RCIN (i.e., chronic renal insufficiency, congestive heart failure, diabetes mellitus, and arterial hypertension), pre-existing renal ischemia with elevation of the renal vascular resistance is a common feature (12).

Radiocontrast media may induce increased oxygen consumption due to their osmotic load, because the oxygen consumption is related to the Na/K-ATPase activity, which is the driving force for the transepithelial electrolyte and water transport. It has been claimed that increased adenosine levels as a result of enhanced ATP hydrolysis may be a major factor in the development of acute renal failure after radiocontrast media application, because RCM application increases urinary adenosine (17) and treatment with an adenosine antagonist has been shown to prevent RCIN (17,18). This hypothesis of an adenosine-mediated renal response to RCM is supported by the observation that dipyrindamide, a nucleoside uptake blocker, increases the renal hemodynamic effects of contrast media (17,18). In addition, there are some similarities between RCIN and adenosine-induced renal hemodynamic changes. (1) Sodium depletion is known to potentiate adenosine action within the kidney (24) and also to potentiate the nephrotoxicity of RCM (25,26). (2) Blockade of the production of vasodilative prostaglandins by indomethacin increases both the adenosine effect in the kidney (27) and RCM-induced vasoconstriction (10,11,19). (3) Ischemia before RCM application increases renal toxicity (6,7), which also has been shown for the adenosine response of the kidney (28,29). (4) RCM and adenosine both showed disparate effects regarding regional blood of the kidney with medullary vasodilation (11,16).

Experimental studies in different animal models of acute renal failure revealed a nephroprotective effect of adenosine antagonism (18,30-35). Studies in dogs showed a nephroprotective effect of theophylline after RCM application (17). Preliminary results in humans also indicate a nephroprotective effect of theophylline concerning the reduction of GFR after application of RCM (2,36). These favorable effects of theophylline are believed to be due to its role as an adenosine antagonist (17,37). Theophylline concentrations in the millimolar range exhibit an inhibitory effect on the phosphodiesterase (37,38). However, the concentrations of theophylline in the micromolar range that we used act primarily as a competitive antagonist of adenosine binding at membrane fragments (17,37,38). The numerous biologic effects of adenosine are mediated primarily by either the A1 or A2 subtypes of the adenosine receptor (39). The main effects of adenosine in the kidney occur via activation of the A1 adenosine receptor (39). Recently published studies report a significant improvement of kidney function with the use of an adenosine A1-receptor antagonist in various models of acute renal injury (40-44). Hence, we decided to compare the effects of theophylline, an unspecific adenosine antagonist, with those of DPCPX, a specific A1 adenosine receptor antagonist, to specify the main adenosine actions in the kidney with regard to RCIN. After treatment with both adenosine receptor antagonists, no change in GFR or RBF could be demonstrated in L-NAME rats in contrast to results obtained in the control group (Table 1, Figure 5), indicating a nephroprotective effect of adenosine.

Figure 5. Intraindividual change of GFR and RBF at the end of the study compared with baseline in all groups (*P < 0.05; **P < 0.01).
antagonism in this model of RCIN. Because theophylline and DPCPX showed the same nephroprotective effect regarding the prevention of GFR and RBF decline in our chronically NO-deficient rats, one may assume that inhibition of the A<sub>1</sub> adenosine receptor constitutes the main mechanism of nephroprotection. Whether other vasodilating substances would be able to exert the same positive effect in this animal model of RCIN remains to be shown. Besides adenosine, other vasoactive substances have been shown to be involved in RCIN, such as endothelin, renin, angiotensin II, and norpinephrine (1,13,14,19,45).

In conclusion, chronic NO blockade resulted in a higher sensitivity regarding hemodynamic changes induced by contrast media. These hemodynamic effects can be attenuated by adenosine antagonists.

References
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