Adenosine-induced renal vasoconstriction in diabetes mellitus rats: role of prostaglandins

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The renal vascular response to adenosine is unique in that adenosine induces vasoconstriction of the afferent glomerular arteriole via adenosine A1 receptors (19, 22), in contrast to other vascular beds in which adenosine acts as a vasodilator. A number of factors and conditions modify the renal vasconstrictor response to adenosine, including sodium intake, renal arterial perfusion pressure, ureteral obstruction, nitric oxide, prostaglandins, and diabetes mellitus (19, 21, 22). In a previous study, we demonstrated an increased vasoconstrictive sensitivity of the renal vasculature to endogenous and exogenous adenosine in streptozotocin (STZ)-induced diabetic rats (22). The effects of adenosine on the renal vasculature in that study were mediated via adenosine A1 receptors because they were inhibited in a dose-dependent manner by the selective adenosine A1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) (22).

Prostaglandins modulate renal function, including tubular transport and vascular hemodynamics (6). Vasodilatory prostaglandins, such as PGE2 and PG12, regulate pre- and postglomerular tone, antagonizing renal vasoconstriction (9).

In diabetic patients and animals with experimental diabetes mellitus, several studies report alterations of renal prostaglandin synthesis (3, 13, 16, 24, 27). Both increases (3, 8, 24, 27) and decreases (13, 16) of vasodilating prostaglandin synthesis have been reported in the diabetic kidney. The diabetic renal vasculature is characterized by dysfunction of its vasodilator capacity (5, 7, 14). There is considerable evidence indicating that the extrarenal (18) and renal (14) endothelial-dependent vasodilation mediated by prostaglandins is impaired in humans and animals with diabetes mellitus, but the overall role of prostaglandin-dependent renal vasodilation in diabetes remains controversial.

Therefore, in the present study, we determined the sensitivity of the renal vasculature to adenosine during inhibition of prostaglandin synthesis and the generation of renal PGE2 in STZ-induced diabetes mellitus.

MATERIAL AND METHODS

The renal vascular response to adenosine on renal blood flow (RBF) was studied during the inhibition of prostaglandin synthesis by indomethacin (Indo) in nondiabetic control and STZ-diabetic rats. The response to exogenous adenosine was determined by injecting adenosine via a catheter placed into the abdominal aorta, which reduced RBF in a dose-dependent manner. The vascular response to endogenous adenosine was assessed by quantification of the postocclusive reduction of RBF (POR), a phenomenon shown to be mediated by adenosine A1 receptors (22).

Animal Preparation

To provide physiological conditions in nonstressed animals, experiments were performed in nonfasted male Sprague-Dawley rats; the animals had free access to a regular rat pellet diet and tap water until the morning of the experiments. The rats were anesthetized with thiopental intraperitoneally (Trapanal; Byk-Gulden) with a dose of 100 mg/kg. The animals were placed on a heated table to maintain body temperature at 37°C via a servo-controlled rectal thermometer. Respiration was spontaneous through an endotracheal...
tube. Two catheters were inserted into the right jugular vein. One catheter served for continuous infusion of isotonic saline (0.9 g/dl) at a rate of 2 ml/h, the other catheter served for vehicle or drug administration with a continuous infusion of isotonic saline (0.9 g/dl) at a rate of 1 ml/h. A polyethylene catheter was advanced through the left carotid artery into the abdominal aorta. This aortic catheter was made out of a PE-350, which was heated over a flame and extended to a final outside diameter of 0.8–1.0 mm. The tip of the catheter was positioned 2–3 mm above the renal artery and connected to a microinjection device for manually time-controlled (0.3–0.5 s) 30-µl bolus injection of adenosine. Care was exercised in maintaining the tip of the catheter precisely at its position. In previous experiments, the authors have shown (unpublished data) that by positioning the tip of the catheter 2–3 mm above the renal artery, the highest effective dose of adenosine administered by this technique effectively enters the renal microcirculation. Positioning the tip of the catheter further above or closer to the renal artery branch showed a lesser effect of the adenosine-induced reduction of RBF. Arterial blood pressure was continuously monitored via a right femoral artery catheter connected to a Statham pressure transducer. The heart rate was derived from the pressure tracing connected to a thermoprinter (WK-280 R; Foehr Medical Instruments). The left kidney was exposed by a subcostal flank incision and placed in a Lucite holder. After careful preparation of the kidney hilus, a flow probe was fitted around the renal artery and connected to an electromagnetic flowmeter (model 501; Carolina Medical Electronics) for continuous monitoring of RBF. Calibration of zero flow was confirmed by occluding the renal artery distal to the flow probe. The abdominal cavity was covered by a sheet of Parafilm (Laboratory Film, American National Can) to prevent evaporation of fluid. Urine from the left kidney was collected via a ureteral catheter, and the bladder was cannulated for free drainage of urine from the right kidney. The rats were allowed to stabilize after the surgical procedure for 60 min.

**Experimental Insulin-Dependent Diabetes Mellitus**

The animal model of insulin-dependent diabetes mellitus (IDDM) was achieved by an intraperitoneal injection of 50 mg/kg STZ (Sigma) dissolved in sodium citrate buffer (pH 4.2). Tail blood samples taken 3 days after STZ injection and on the day of the experiment provided measurements of blood glucose levels. Animals with a blood glucose <250 mg/dl were not included in the experimental series. The experiments started 6–8 wk after STZ administration, and nondiabetic rats served as controls. The 50-mg/kg STZ model of IDDM was chosen to reduce malnourishment, catabolic state, weight loss, and hyperphagia, because the administered dose of STZ does not completely destroy all beta islet cells of the rat pancreas (28) and a remaining small basal insulin production is achieved with this IDDM model. Furthermore, moderate hyperglycemia was stable until the day of the experiment (blood glucose levels 3 days after STZ, 319 ± 12 mg/dl; on the day of the experiment, 346 ± 27 mg/dl).

The progression of diabetic nephropathy is attributed basically to hyperglycemia and insulin deficiency (15); hence, the diabetic model of the current study without insulin treatment may represent a more progressive state of the development of diabetic nephropathy than comparable models with insulin treatment. Consequently, the presented findings may be restricted to STZ-induced diabetes mellitus without insulin treatment.

**Exogenous Adenosine**

Exogenous adenosine (Serva), dissolved in 0.90 g/dl NaCl, was given in sequentially increasing doses, starting from 0.01 nmol and increasing to 100 nmol, with 3–5 min between doses. Adenosine was administered via the aortic catheter in a bolus of 30 µl over 0.3–0.5 s. Adenosine bolus injections (0.01 up to 10 nmol) did not affect arterial blood pressure; higher doses (30–100 nmol) of adenosine bolus injections slightly decreased arterial blood pressure, however, only after the RBF response was almost complete. Vehicle bolus injections with isotonic saline did not result in any change of RBF.

The reduction of RBF (ΔRBF) due to adenosine injections was assessed as the difference of minimal postinjection RBF (RBFmin) to baseline RBF (RBFbaseline) as a percentage of the preinjection RBF (= RBFbaseline)

\[
\Delta RBF = \frac{RBF_{baseline} - RBF_{min}}{RBF_{baseline}}
\]

The percentage of RBF reduction (ΔRBF%) in response to adenosine injections (0.01–100 nmol) was plotted in graphs as dose response curves. RBF measurements were performed by means of an electromagnetic flowmeter fitted around the left renal artery in a pulsatile fashion, because RBF changes occurred within a time range of a tenth of a second. These RBF changes cannot be observed when the pulsatile recordings are dampened. In the pulsatile RBF measurement, RBF pulse curves interfere with the precise measurement of very small RBF reductions. The pulsatile amplitude of the basal RBF tracing usually ranges from 17 to 20% of basal RBF; hence, the minimal precise detectable RBF reduction with the pulsatile RBF registration should be 17–20% ΔRBF. Under conditions in which the minimal dose of adenosine (e.g., 0.01 nmol) did not reach the minimal detectable RBF reduction (at least 20%), the dose response curve was extrapolated to calculate the ED50.

**Endogenous Adenosine**

The renal response to endogenous adenosine was assessed by the POR as described previously (22). In brief, POR was determined by release of two to three occlusions (30 s) of the renal artery. During renal artery occlusion, renal adenosine generation increases by hydrolysis of ATP (21). After release of the renal artery occlusion, the accumulated adenosine causes vasoconstriction of the afferent arterioles via adenosine A1-receptor stimulation, which is apparent in the POR as described previously (22). In the pulsatile RBF measurement, the POR after release of a renal artery clamp is mediated by adenosine A1-receptor stimulation and can be inhibited in a dose-dependent manner with the highly selective adenosine A1-receptor antagonist RIB-11 (23).

**Nondiabetic CON-Rat**

**Diabetic STZ-Rat**

![Fig. 1](http://ajpregu.physiology.org/)

**Fig. 1.** Original tracing of postocclusive reduction of renal blood flow (POR) after release of a 30-s renal artery occlusion clamp in a nondiabetic control (CON) rat (left) and in a diabetic streptozotocin (STZ) rat (right). RBF, renal blood flow.
intrarenal PGE2 synthesis as described by Baranowski and A recovery period of 8–10 min followed each occlusion. indomethacin (Indo).

adenosine (POR) in presence of a normal saline vehicle and after

sine was determined.

The renal response to exogenous and endogenous adenosine was assessed with an isotonic normal saline vehicle. Then 1 ml of alkaline saline (pH 8) was intravenously infused over 15 min, and the renal response to exogenous and endogenous adenosine was determined.

Group 4: Effect of alkaline saline vehicle of Indo on the renal vascular response to adenosine in STZ rats. The protocol of this group was identical to group 5, but in STZ rats (n = 5).

Analytic Methods

Blood glucose levels were measured with a blood glucose meter (One Touch, Lifescan) 3 days after STZ injection and on the day of the experiment after the equilibration period. Glomerular filtration rate (GFR) was calculated on the basis of the clearance of inulin. Inulin in plasma and urine was measured by the Anthrone method (11). Sodium concentrations in plasma and urine were measured by using a flame photometer (IL 943 Flame Photometer, Instrumentation Laboratory). Renal interstitial fluid PGE2 levels in the dialysate samples and urinary PGE2 levels were measured by an enzymatic immunoassay (Cayman Chemical, Ann Arbor, M1).

Statistical Analysis

Data were expressed as means ± SE. Two-factor ANOVA, with repeated measures on one and unpaired Student’s t-test, were performed as appropriate. Statistical analysis of the ED50 values was performed by the Tukey-Kramer multiple comparisons test. P < 0.05 was considered significant.

RESULTS

Exogenous Adenosine

There were no significant differences between control, STZ, and time-vehicle control rats with respect to baseline values for mean arterial blood pressure, heart rate, RBF, and hematocrit (see Tables 1 and 2). In STZ-diabetic rats, the adenosine-induced reduction of RBF was markedly potentiated compared with control rats. One nanomole adenosine injected into the abdominal aorta decreased RBF by −68.1 ± 6.0% in STZ rats and by −24 ± 1.2% in control rats (see Fig. 3, A and B). The calculated ED50 of adenosine was significantly greater (P < 0.001) in control rats (5.5 ± 0.51 nmol) compared with STZ rats (0.32 ± 0.03 nmol). Hence, the dose response curve of RBF reduction by single injec-

Fig. 2. Experimental protocol of renal response to exogenous adenosine (single injections of adenosine, 0.03–100 nmol) and endogenous adenosine (POR) in presence of a normal saline vehicle and after bolus infusion of indomethacin (Indo).
tions of adenosine was shifted to the left by a factor of 20 in STZ rats compared with the dose response curve of control rats.

Effects of Indo on the adenosine-induced renal vasocostriction. The ED$_{50}$ of adenosine was 5.5 ± 0.6 nmol in control rats with the vehicle and 0.55 ± 0.07 nmol adenosine with Indo. This presents a significant (P < 0.001) left shift of the dose response curve of control rats with Indo by a factor of 10. In STZ rats, however, Indo shifted the dose response curve to the left only by a factor of two, which was not significant (from ED$_{50}$ of 0.32 ± 0.03 nmol adenosine to ED$_{50}$ of 0.16 ± 0.02 nmol adenosine, P > 0.05). Hence, the effects of Indo to increase the responsiveness to the adenosine-induced renal vasocostriction were attenuated in STZ rats (Fig. 3, A and B). The ED$_{50}$ of control rats with Indo (0.55 ± 0.07 nmol adenosine) was similar to the ED$_{50}$ of STZ rats with the vehicle (0.32 ± 0.03 nmol adenosine) and not significantly different (P > 0.05).

Endogenous Adenosine

Effects of Indo on the POR. The renal vascular response to endogenous adenosine, assessed by POR, was significantly enhanced (P < 0.01) in STZ rats compared with control rats (Figs. 2 and 4). Indo increased the baseline POR by 56% in control rats but did not change baseline POR in STZ rats (see Table 1).

Table 2. Summary of data characterizing 2 experimental groups, control and STZ rats

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 16)</th>
<th>STZ Rats (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, wk</td>
<td>13 ± 2</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>Body wt, g</td>
<td>391 ± 12</td>
<td>358 ± 16</td>
</tr>
<tr>
<td>Kidney wt, g</td>
<td>1.93 ± 0.3</td>
<td>2.45 ± 0.2*</td>
</tr>
<tr>
<td>Kidney wt, g/100 g body wt</td>
<td>0.598 ± 0.02</td>
<td>0.651 ± 0.1</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>46.8 ± 0.5</td>
<td>47.5 ± 0.6</td>
</tr>
<tr>
<td>Blood glucose, mg/dl, 3 days after STZ injection</td>
<td>92.6 ± 5</td>
<td>319 ± 12†</td>
</tr>
<tr>
<td>Blood glucose, mg/dl, day of experiment</td>
<td>89 ± 5</td>
<td>346 ± 26†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Summary of data characterizing 2 experimental groups, nondiabetic control and STZ-diabetic rats. *P < 0.05 and †P < 0.001, comparison between nondiabetic control and STZ-diabetic animals.
Time and Vehicle Controls

There was no time-dependent effect on the POR in control and STZ rats. The vehicle of Indo in control (group 3) and STZ (group 4) rats did not affect mean arterial blood pressure (control rats, 98.5 ± 4.2 mmHg; STZ, 92.8 ± 5.8 mmHg), heart rate (control rats, 360 ± 10.2 beats/min; STZ, 363 ± 8.7 beats/min), and RBF (control rats, 4.5 ± 0.2 ml/min; STZ, 4.3 ± 0.2 ml/min). The results demonstrate that the potentiation of the renal response to adenosine with Indo in control and STZ rats was unrelated to time- and vehicle-dependent effects.

Renal Cortical, Medullary, and Urinary PGE$_2$

The PGE$_2$ data of the dialysate were not corrected for recovery. PGE$_2$ dialysate concentrations of the cortex and medulla and urinary PGE$_2$ excretion tended to be higher in STZ rats (cortex: 169 ± 61 pg/ml; medulla: 640 ± 88 pg/ml; urine: 138 ± 25 pg/min) compared with control rats (cortex: 99 ± 12 pg/ml; medulla: 489 ± 107 pg/ml; urine: 82 ± 28 pg/min). The differences of PGE$_2$ concentrations and excretions between STZ and control were not statistically significant. PGE$_2$ dialysate concentrations of the medulla were significantly higher compared with the cortex in both groups, STZ and control rats. Indo (10 mg/kg) decreased dialysate PGE$_2$ concentrations in the cortex and medulla and urinary PGE$_2$ excretion in both groups, STZ (cortex: 8 ± 2 pg/ml; medulla: 14 ± 3 pg/ml; urine: 30 ± 5 pg/min) and control rats (cortex: 17 ± 1 pg/ml; medulla: 30 ± 7 pg/ml; urine: 20 ± 2 pg/min; see Fig. 5).

In control rats, Indo infusion did not significantly change mean arterial pressure (vehicle: 126 ± 9 mmHg; Indo: 122 ± 8 mmHg), GFR (vehicle: 2.9 ± 0.1 ml/min; Indo: 3.2 ± 0.3 ml/min), urine flow (vehicle: 32 ± 9 ml/h; Indo: 53 ± 19 ml/min), and fractional sodium (vehicle: 0.8 ± 0.4%; Indo: 1.8 ± 1.4%). In STZ rats, Indo infusion did not significantly change mean arterial pressure (vehicle: 129 ± 4 mmHg; Indo: 123 ± 4 mmHg), GFR (vehicle: 2.4 ± 0.4 ml/min; Indo: 2.0 ± 0.4 ml/min), urine flow (vehicle: 31 ± 5 ml/h; Indo: 17 ± 2 ml/min), and fractional sodium (vehicle: 0.6 ± 0.1%; Indo: 0.5 ± 0.1%).

DISCUSSION

Enhanced adenosine-induced renal vasoconstriction in STZ-diabetic rats. The present findings show that the adenosine-induced renal vasoconstriction was markedly enhanced in STZ rats compared with control rats. Adenosine (1 nmol) injected into the abdominal aorta caused a markedly greater reduction of RBF in STZ rats compared with control rats. Because intrarenal adenosine generation may cause a different renal vascular response than single injections of adenosine, the generation of endogenous adenosine was assessed by a 30-s renal artery occlusion. This resembles a more continuous adenosine generation, and again there was...
a markedly greater reduction and duration of RBF in STZ rats compared with control rats. During renal ischemia, e.g., renal artery occlusion, adenosine generation is increased by hydrolysis of ATP to adenosine throughout the kidney (21, 22). The accumulated renal adenosine stimulates A<sub>1</sub> receptors on the afferent arteriole and causes renal vasoconstriction as manifested in the POR (22). The diabetic kidney has been shown to have a much higher susceptibility to ischemic periods, e.g., renal artery occlusion, which eventually may lead to diabetic nephropathy (20, 22). Hence, an increased sensitivity to adenosine-induced renal vasoconstriction may be one of the pathophysiological mechanisms responsible for the higher susceptibility of the diabetic kidney to ischemia. Because the POR is an adenosine A<sub>1</sub> receptor-mediated phenomenon (22), increased adenosine A<sub>1</sub> receptor density could potentially contribute to the increased sensitivity of the diabetic renal vasculature to adenosine. However, adenosine A<sub>1</sub> receptor density was not increased in glomeruli of STZ rats compared with control rats (1), thus other factors, including a diminished prostaglandin-dependent vasodilator capacity of the diabetic renal vasculature to counteract the renal vasoconstrictor action of adenosine, may account for the increased sensitivity of the diabetic kidney to adenosine. We, therefore, investigated the RBF response to adenosine in the presence of prostaglandin synthesis inhibition in control and STZ-diabetic rats.

Attenuated Effect of Inhibition of Prostaglandin Synthesis (Indo) on the Adenosine-Induced Renal Vasoconstriction in STZ-Diabetic Rats

In the present studies, the inhibition of prostaglandin synthesis by Indo markedly potentiates the adenosine-induced renal vasoconstriction in control rats but not in STZ-diabetic rats. Indo increased the POR in control rats after a 30-s renal artery occlusion, suggesting that during renal ischemia vasodilating prostaglandins counteract the endogenous adenosine-induced renal vasoconstriction.

The RBF reduction by single injections of adenosine was markedly enhanced in the presence of Indo in control rats, indicated by a left shift of the dose–response curve by factor 10. This suggests that prostaglandins also counterbalance the vasoconstrictive effects of exogenous adenosine in control rats. Similar findings have been observed with ANG II (26). In these studies, cyclooxygenase inhibition significantly increased the duration of the renal vasoconstrictor response to intravenous boluses of ANG II and potentiated the renal pressor response to ANG II. Likewise, in humans, aspirin increased the renal vasoconstriction of ANG II (31).

The ED<sub>50</sub> of control rats with Indo was similar to the ED<sub>50</sub> of STZ rats with vehicle, thus the adenosine-induced renal vasoconstriction in STZ rats with vehicle can be mimicked in control rats with Indo. In contrast to control rats, in STZ rats Indo did not change the adenosine-induced renal vasoconstriction. Adenosine injected into the lower abdominal aorta caused a 20% RBF reduction, and Indo did not further increase the adenosine-induced renal vasoconstriction in STZ rats (Fig. 3B), whereas in control rats, Indo increased the adenosine-induced RBF reduction (Fig. 3A). This suggests that the prostaglandin-dependent vasodilator capacity of the afferent arteriole is diminished or dysfunctional in the diabetic renal vasculature. A diminished or dysfunctional prostaglandin-dependent renal vasodilation of the afferent arterioles in STZ-diabetic rats could account for the increased sensitivity of the diabetic renal vasculature to the vasconstrictor potency of adenosine and the attenuated effects of prostaglandin inhibition on the adenosine-induced renal vasoconstriction in STZ rats.

Dysfunction of the Prostaglandin-Dependent Vasodilation in the Diabetic Renal Vasculature

In the current study, 6–8 wk after STZ injection, renal PGE<sub>2</sub> levels in the cortex, medulla, and urine were not decreased in the two groups, STZ and control rats. In both groups, PGE<sub>2</sub> was significantly higher in the renal medulla than in the cortex, indicating its major site of production under normal conditions (30). These findings demonstrate that a prostaglandin deficiency is unlikely to be responsible for the attenuated effects of prostaglandin synthesis inhibition in STZ rats. In addition, other studies also have found that PGE<sub>2</sub> synthesis is not decreased in the diabetic kidney, e.g., in incubated isolated glomeruli from STZ rats 2–3 wk after STZ treatment (3, 24, 27) and in urine of patients with diabetes mellitus (12). However, others have reported decreased generation of renal vasodilating prostaglandins in diabetes mellitus (13, 16). Alterations of renal prostaglandin synthesis in diabetes can probably be in part attributed to the experimental diabetes mellitus model. Renal prostaglandin synthesis in experimental diabetes mellitus likely depends on the duration and on the presence of insulin, because insulin treatment (23) and glucose (17) increased PGE<sub>2</sub> synthesis in STZ rats.

The present findings suggest that generation of renal vasodilating prostaglandins is not diminished in STZ rats and that the responsiveness of the renal vasculature to inhibition of prostaglandin synthesis is attenuated in STZ rats. This suggests that the vascular smooth muscle may be insensitive to vasodilating prostaglandins in diabetic rats. Several factors within the prostaglandin signal transduction pathway could be responsible for a diminished vasodilation of the diabetic vascular smooth muscle cell, including decreased release of cAMP or a defective coupling of the receptor to its effector (29). Furthermore, prostaglandin-dependent renal vasodilation was found to interact with nitric oxide-dependent renal vasodilation (7), which is diminished in diabetes mellitus. Hence, a reduced prostaglandin vasodilating capacity may be linked to a diminished nitric oxide-dependent vasodilation in diabetes. Thus, even though prostaglandin synthesis is not diminished in STZ rats, prostaglandin-dependent renal vasodilation may be diminished or uncoupled from the vascular smooth muscle.
In summary, the present findings show that the diabetic renal vasculature has an increased sensitivity to the adenosine-reduced renal vasoconstriction. The adenosine-induced renal vasoconstriction is increased by inhibition of prostaglandin synthesis in control rats but not in diabetic STZ rats. The observations suggest that the diabetic renal vasculature has a diminished vasodilator capacity in response to prostaglandins to counteract adenosine-induced renal vasoconstriction.

Perspectives

The present observations are of clinical relevance because adenosine has been proposed as a pathophysiological factor in the development of acute renal failure induced by contrast media (4). Contrast media-induced acute renal failure has a higher incidence in diabetic patients with impaired renal function (25). In these situations, renal adenosine is thought to be released during renal ischemic conditions with subsequent effects on the vascular and tubular system of the kidney. Therefore, a defective prostaglandin-dependent renal vasodilator capacity in response to prostaglandins to counteract adenosine-induced renal vasoconstriction may contribute to an increased adenosine-induced renal vasodilation as a pathophysiological factor in contrast media-induced renal failure in diabetes mellitus. Adenosine receptor antagonists may be beneficial in these settings (10).

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