Spontaneously reduced blood pressure load in the rat streptozotocin-induced diabetes model: potential pathogenetic relevance

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Bidani AK, Picken M, Hacioglu R, Williamson G, Griffin KA. Spontaneously reduced blood pressure load in the rat streptozotocin-induced diabetes model: potential pathogenetic relevance. Am J Physiol Renal Physiol 292: F647–F654, 2007. First published September 12, 2006; doi:10.1152/ajprenal.00017.2006.—The rat streptozotocin (STZ)-induced diabetes model is widely used to investigate the pathogenesis of diabetic nephropathy. However, overt nephropathy is inexplicably slow to develop in this model compared with renal mass reduction (RMR) models. To examine whether blood pressure (BP) differences correlated with the time course of glomerulosclerosis (GS), BP was measured continuously throughout the course by radiotelemetry in control (n = 17), partially intrinsically reduced STZ-diabetes (average blood glucose 364 ± 15 mg/dl; n = 15), and two normotensive RMR models (systolic BP < 140 mmHg—uninephrectomy (UNX; n = 16) and 3/4 RMR by surgical excision [right nephrectomy + excision of both poles of left kidney (RK-NX); n = 12]) in Sprague-Dawley rats. Proteinuria and GS were assessed at ∼ 16–20 wk (all groups) and at 36–40 wk (all groups except RK-NX). At 16 wk, significantly greater proteinuria and GS had developed in the RK-NX group compared with the other three groups (not different from each other). By 36–40 wk, substantial proteinuria and GS had also developed in the UNX group, but both the control and the STZ-diabetic rats exhibited comparable modest proteinuria and minimal GS. Systolic BP (mmHg) was significantly reduced in the STZ-diabetic rats (116 ± 1) compared with both control (124 ± 1) and RMR (128 ± 1.2 and 130 ± 3.0) groups (P < 0.01). Similarly, “BP load” as estimated by BP power spectral analysis was also lower in the STZ-diabetic rats. Given the known protective effects of BP reductions on the progression of diabetic nephropathy, it is likely that this spontaneous reduction in ambient BP contributes to the slow development of GS in the STZ-diabetes model compared with the normotensive RMR models.

radiotelemetry; glomerulosclerosis; remnant kidney; hyperfiltration

the progressive nature of chronic kidney disease (CKD) has been intensively investigated over the past two decades with experimental models of renal mass reduction (RMR) and diabetes. Multiple pathogenetic pathways, both hemodynamic (increased glomerular pressures and flows) and nonhemodynamic (dysregulated growth factor and cytokine production, glomerular hypertrophy, and cell dysfunction), have been identified (25, 26, 31, 38, 42, 52). Although the relative contributions of individual mechanisms remain controversial, it is likely that the final triggering of the cellular and molecular mediators of glomerulosclerosis (GS) results from the complex interactions between such pathways (21, 34, 61). In this context, the model of Type 1 diabetes most frequently used to investigate the pathogenesis of diabetic nephropathy is that of suboptimally insulin-treated streptozotocin (STZ)-induced diabetes in the rat (4, 24, 36, 54, 56, 62, 64, 68, 69). Such partial treatment (blood glucose 300–400 mg/dl) reduces osmotic diuresis and weight loss. Moreover, such rats exhibit early hyperperfusion and hyperfiltration similar to those seen in human Type 1 diabetes, as well as substantial increases in glomerular capillary pressures (Pgc) (4, 39, 68, 69). This has led to the postulate that, as in RMR models, hemodynamic injury plays a major role in the pathogenesis of diabetic GS (4, 38, 39, 52, 68, 69). Moreover, kidney and glomerular hypertrophy is common to both RMR states and diabetes, suggesting that nonhemodynamic pathways for GS are also shared (24–26, 31, 36, 42, 56). A similarity in pathogenesis is also suggested by the deleterious effects of a high-protein diet and the protective effects of a low-protein diet on GS in both diabetes and RMR models (14, 33, 49, 52, 56, 69). Additionally, a great deal of in vivo and in vitro evidence indicates the presence of additional nonhemodynamic pathogenetic pathways, particular to hyperglycemia and the diabetic milieu, that are also expected to further potentiate the development of GS (52, 62, 63).

Nevertheless, despite the hemodynamic pathways shared with RMR models and the great abundance of additional nonhemodynamic mechanisms in STZ-diabetes, significant histological GS is still very slow (> 1 yr) to develop compared with the RMR models (4, 31, 36, 52, 56, 60, 68, 69), for reasons that have remained largely obscure because most investigations have focused on defining mechanisms that promote GS rather than those that might retard the in vivo development of GS in this model. Given that even modest elevations in blood pressure (BP) have been shown to accelerate, and BP reductions to slow, the development and progression of both experimental and clinical diabetic and nondiabetic nephropathies (6, 9, 10, 41, 52, 56), the present studies were performed to examine whether differences in ambient “BP load” may account for differences in the time course of development of GS in these models. Although tail-cuff BP measurements have shown high normal or moderately elevated BP in STZ-diabetes, the data have been inconsistent and often discrepant with direct BP measurements (4, 46, 60, 69). In view of the now clearly demonstrated limitations of the tail-cuff method (9, 13, 27–30, 45), continuous chronic BP radio-telemetry for ∼ 40 wk was utilized to examine the relationship

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between BP load and the development of proteinuria and GS in the partially insulin-treated STZ-diabetes model compared with concurrently followed control rats and two normotensive models (systolic BP <140 mmHg) of graded RMR [uninephrectomy (UNX) and ~3/4 RMR by surgical excision (RK-NX)] (12, 28, 31, 32). BP load was additionally assessed with BP power spectral analysis. Such analysis can be used to estimate and separate the BP power (energy/unit time) as consisting of two primary components, that due to its mean value (DC BP power) and that due to its fluctuations from the mean because of the heartbeat and other slower neurohormonal mechanisms (AC BP power) (1, 11, 12, 37).

**MATERIALS AND METHODS**

Eight-week-old male Sprague-Dawley rats (~250 g), cared for in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, were fed a standard diet and divided into four groups after baseline measurements of 24-h protein excretion rates by the quantitative sulfosalicylic acid method (9, 13, 14, 27–33). For controls, rats underwent sham RMR surgery. For partially insulin-treated diabetes, intravenous STZ (65 mg/kg) was administered through the tail vein. After confirmation of diabetes 72 h later (initial blood glucose in all diabetic rats exceeded 300 mg/dl), Alza osmotic pumps were installed subcutaneously to deliver insulin calculated to maintain blood glucose at 300 – 400 mg/dl (55). Blood glucose monitoring and Alza pump and insulin dose changes were performed at 4-wk intervals (blood glucose values ranged between 175 and 525 mg/dl and insulin doses between 3 and 5 U·kg⁻¹·day⁻¹). For UNX, the right kidney was surgically removed. For RK-NX, the right kidney and both poles of the left kidney were surgically excised (28, 31, 32). Rats were followed for either 16–20 wk before termination (all 4 groups) or for 36–40 wk (control, UNX, and STZ-diabetes groups only, because all RK-NX rats were killed at 16–20 wk). During the last week before death, proteinuria was measured again; the rats were then euthanized, primarily because of infection and technical problems, which are not included in the presented results (6 diabetic, 2 RK-NX, 1 UNX, and 1 control).

**BP radiotelemetry.** The rats were prepared for BP radiotelemetry (Data Sciences) as previously described (9, 13, 28–33) at the time of sham or RMR surgery or in the case of STZ-diabetes at the time of the initial installation of Alza (insulin) pumps. Each rat had a BP sensor (model TA11PA-C40) inserted into the aorta below the level of the renal arteries, and the radiofrequency transmitter was fixed to the peritoneum. The rats were housed individually in plastic cages placed on top of the receiver. Systolic BP was continuously recorded at 10-min intervals with the Lab Pro Data Acquisition System, with each BP reading representing the average of ~60 readings during a 10-s interval as previously described (9, 13, 28–33). Additionally, one to three separate BP recordings at a sampling rate of >20 Hz over 24 h were obtained for analysis of BP power spectra in several rats from each group between the 8th and 16th weeks. Because significant differences were not observed for different recordings from an individual rat, the data were averaged for each rat before statistical analysis. The BP recordings obtained at >20 Hz were digitally resampled to 20 Hz after low-pass filtering to prevent aliasing. After detrending, power spectra were determined with fast Fourier transforms and Welch’s averaged periodogram method (50% overlap of segments and a Hanning window applied) as previously described (1, 12). To investigate the possible impact of circadian rhythms in BP, we conducted similar spectral analyses for each of four nonoverlapping 6-h periods within the 24-h data records, with the first period commencing at 12 AM. Although average BP and low-frequency power were a little higher at night, no strong differences in distribution of BP spectra were evident over the circadian cycle. Accordingly, the overall 24-h spectrum presented was considered to be representative of the BP load.

Additionally, heart rate was determined from the 24-h BP recordings. Individual heartbeats were determined from the sampled BP waveform by locating the peak pressure during systole and the minimal pressure during diastole. The average heart rate was then calculated by dividing the total number of heartbeats occurring during the recording by the length of time of the recording.

**Histology.** Transverse sections through the papilla were cut at a thickness of ~3–4 μm and stained with hematoxylin and eosin and periodic acid-Schiff. At least 100 glomeruli were examined in each animal, and the percentage of glomeruli exhibiting clear histological evidence of segmental or global GS was estimated in a blinded fashion with standard morphological criteria as previously described (9, 13, 14, 28–33, 59). Additionally, a separate semiquantitation of mesangial matrix expansion and of GS was performed at 36–40 wk in the control and STZ-diabetic rats with the criteria and scoring methods described by Raji et al. (59).

**Statistical analyses.** Analysis of variance followed by Student-Newman-Keuls test or by Kruskall-Wallis nonparametric analysis of variance followed by Dunn’s multiple comparison tests were used, as appropriate, to examine the differences between the groups (67). Because the GS data were not normally distributed, they were log transformed for statistical analysis. A P > 0.05 was considered not significant. Results are means ± SE.

**RESULTS**

Table 1 provides the initial and follow-up body weights at 16–20 wk for all four groups and at 36–40 wk for the remaining rats from the control, UNX, and STZ-diabetes groups. The initial body weights were not different, but the body weights of the STZ-diabetic rats were significantly lower at both the 16–20 wk and 36–40 wk time points. Average monthly blood glucose levels for all STZ-diabetic rats in the study were 364 ± 15 mg/dl (403 ± 23 mg/dl for the 6 rats followed for 16–20 wk and 338 ± 15 mg/dl for the 9 rats followed for 36–40 wk). Table 1 also presents the course of proteinuria in all groups. Baseline proteinuria was not significantly different between the groups. Although it increased with time in all groups, the increases in the RK-NX group at 16–20 wk were significantly greater than those in the other three groups, which were not significantly different from each other. Likewise, by 36–40 wk proteinuria was significantly greater in the UNX rats compared with the control and STZ-diabetic rats, which still did not show significant differences between them.

Figure 1 shows that a pattern essentially identical to that for proteinuria was observed for GS. A significantly greater percentage of glomeruli exhibited GS in the RK-NX group at 16–20 wk compared with the other three groups, which were not different from each other. By 36–40 wk, the UNX rats had developed significantly greater %GS than the control and STZ-diabetes groups, which did not differ significantly. In contrast to the lack of significant differences for both proteinuria and %GS between the STZ-diabetes and control rats, when mesangial matrix expansion and GS were quantitated separately in these groups at 36–40 wk with the scoring system of Raji et al. (59) a significantly higher score was obtained for mesangial matrix expansion in diabetic compared with control rats (32 ± 3 vs. 19 ± 3, respectively; P < 0.01) but not for GS (7.3 ± 1.9 vs. 4.8 ± 1.1). Figure 1 also shows that the
Table 1. Course of body weights and proteinuria

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Body wt, g</th>
<th>Proteinuria, mg/24 h</th>
<th>Body wt, g</th>
<th>Proteinuria, mg/24 h</th>
<th>Body wt, g</th>
<th>Proteinuria, mg/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>17</td>
<td>258±6</td>
<td>2.6±0.4</td>
<td>635±10</td>
<td>15.3±2.1</td>
<td>752±30</td>
<td>30.4±4.7</td>
</tr>
<tr>
<td>STZ DM</td>
<td>15</td>
<td>259±6</td>
<td>2.3±0.3</td>
<td>403±23*</td>
<td>18.1±1.7</td>
<td>459±29*</td>
<td>31.1±3.1</td>
</tr>
<tr>
<td>UNX</td>
<td>16</td>
<td>271±4</td>
<td>2.7±0.3</td>
<td>609±22</td>
<td>20.4±3.6</td>
<td>690±25</td>
<td>73.5±11.5*</td>
</tr>
<tr>
<td>RK-NX</td>
<td>12</td>
<td>264±8</td>
<td>2.5±0.4</td>
<td>587±14</td>
<td>58.1±7.6*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are means ± SE for n rats. STZ DM, streptozotocin-induced diabetes; UNX, uninephrectomy; RK-NX, 3/4 renal mass reduction by surgical excision.

*P < 0.01 maximum, compared with all other groups.

time-averaged overall systolic BP of rats with STZ-diabetes for the entire course was significantly lower than that for the other three groups (an average of ~20,000 individual BP readings for the rats followed for 16–20 wk and ~40,000 such BP readings for the rats followed for 36–40 wk). However, the time-averaged systolic BP for the two RMR groups, although higher, was not significantly different from that of the control rats.

An illustration of the course of systolic BP in an individual rat with STZ-diabetes over ~38 wk is provided in Fig. 2A, while Fig. 2B presents the group data. Four-week averages in each rat (~4,000 BP readings) were calculated and meant for each group. As can be noted, systolic BP was significantly lower in the STZ-diabetic rats at most time points during the course of the study. Figure 3 shows the BP power spectra for the control, STZ-diabetes, and UNX groups. For clarity, the data for total AC BP power (0.006 – 8 Hz) as well as that for the heartbeat frequency are shown. The power spectrum for the RK-NX rats is not shown in Fig. 3, but the power spectrum for the RK-NX rats is shown in Fig. 4.

Because of the 1/frequency pattern of AC BP power at frequencies less than the heartbeat frequency, most of the AC BP power is accounted for in this frequency range (Fig. 4). As can be noted from Fig. 4, significantly less total AC BP power was present in the STZ-diabetic rats compared with all other groups, as was also true at frequencies less than the heartbeat frequency. However, at the heartbeat frequency, statistical significance for the differences was only achieved between the STZ-diabetes and the RK-NX group. Similarly, mean BP (DC BP power) was significantly lower (P < 0.01) in the STZ-diabetic rats during these 24-h recordings (92.9 ± 2.3 mmHg) compared with RK-NX (115.4 ± 5.2 mmHg) and UNX (103.9 ± 2.2 mmHg) rats, but the difference with the control rats (100.6 ± 2.5 mmHg) did not reach statistical significance (P < 0.07).

Of interest, the heart rate determined from these 24-h BP recordings obtained at 200 Hz showed that, despite the lower mean BP, heart rate in the STZ-diabetes group (312 ± 8.6 beats/min) was significantly lower compared with the control group (344 ± 7.4 beats/min; P < 0.01) as well as the two RMR
models may not be strictly comparable. Rats with STZ-diabetes have been noted to exhibit not only the increases in glomerular size, pressure, and flows that are postulated to lead to GS in RMR models even in the absence of diabetes (4, 9, 12, 24, 31, 36, 39, 60, 68, 69), but also an abundance of additional superimposed nonhemodynamic mechanisms, believed to be triggered by hyperglycemia and/or the associated diabetic milieu. These include an increased activity of the local renin-angiotensin system (RAS); increased oxidative stress and endothelial dysfunction; increased production, expression, or activity of multiple cytokines and growth factors such as transforming growth factor-β, platelet-derived growth factor, connective tissue growth factor, and vascular endothelial growth factor; altered glomerular cell metabolism and signal transduction pathways including increased activation of protein kinase C; increased production of advanced glycation end products; and increased production and/or decreased degradation of extracellular matrix components (16, 43, 53, 56, 62, 63).

In any event, consistent with the postulated pathogenic role of hemodynamic mechanisms, increased RMR in the present study was associated with a progressive acceleration of GS (RK-NX > UNX > control). The proportionately greater vasodilation of the remnant preglomerular vasculature that we (10, 12, 28, 31, 32) and others (38, 52) have previously documented as a part of the compensatory adaptive response is expected to result in greater fractional glomerular transmission of systemic BP. Moreover, ≥3/4 RMR not only results in greater preglomerular vasodilation but also impairs renal autoregulation that normally protects against the glomerular transmission of BP increases, episodic or sustained, thereby further enhancing the vulnerability to hypertensive injury (10, 12, 14, 28, 30, 32). Accordingly, when severe RMR is accompanied by hypertension (5/6 renal ablation by infarction), GS is greatly accelerated and develops within 6 wk instead of the 16–20 wk in the normotensive surgical excision model (9, 14, 28, 32). In contrast, UNX, at least in the absence of other concurrent renal disease, is associated with preserved autoregulation and only a relatively modest increase in the susceptibility to GS (8, 10, 12, 51). For instance, it still takes ~8 mo for significant GS to develop after UNX in the spontaneously hypertensive rat (SHR) strain (23). Setting aside the contradic-

groups (UNX 339 ± 5.9 beats/min; RK-NX 337 ± 2.9 beats/min; P < 0.05). The control and RMR groups were not significantly different from each other.

DISCUSSION

The rat STZ-induced diabetes model of Type 1 diabetes has been used extensively to investigate the pathogenesis of diabetic nephropathy. However, it has long been recognized that significant overt nephropathy is exceedingly slow to develop in this model, although increases in albuminuria, mesangial matrix expansion, glomerular basement membrane thickening, and/or other surrogate end points are noted at earlier time points (4, 24, 36, 39, 49, 54, 56, 60, 62, 64, 68, 69). Consistent with such data, significant mesangial matrix expansion was observed after 10 mo in STZ-diabetes compared with control rats. Nevertheless, there was a minimal loss of glomerular capillaries and GS was not different between the STZ-diabetes and control rats. The slow development of GS in the present studies is therefore consistent with other long-term studies that have utilized similar histological criteria for defining GS (57, 59). For instance, after 14 mo of partially treated STZ-diabetes (average blood glucose 300–400 mg/dl) in Munich-Wistar rats fed a standard protein diet, GS was only observed in ~6% of the glomeruli by Zatz et al. (68). Likewise, GS in only ~12% of the glomeruli was observed after an even longer follow-up of 16 mo by Anderson et al. (4) in the same strain. Similarly, GS in 9.6% of the glomeruli was reported by Remuzzi et al. (60) after 12 mo of STZ-diabetes in Sprague-Dawley rats. A similar lack of GS, although not as precisely quantitated, has also been noted in other long-term studies (24, 36, 49, 56). Likewise, the time course for the development of GS after UNX in the present studies is also similar to that reported previously (8, 51).

This slower development of GS in STZ-diabetes compared with normotensive RMR models (systolic BP <140 mmHg) is not readily explained, even allowing for the fact that these models may not be strictly comparable. Rats with STZ-diabe-
tory results regarding renal autoregulatory impairment in experimental diabetes (17), at the very least a susceptibility to GS in STZ-diabetes comparable to that after UNX would be expected, particularly given the presence of additional nonhemodynamic mechanisms in diabetes. In fact, micropuncture measurements of $P_{\text{GC}}$ in STZ-diabetes in several studies have shown a $P_{\text{GC}}$ of $\sim 60$ mmHg, which is higher than that reported after UNX ($\sim 55$ mmHg) and almost as high as in the conventional 5/6 ablation model ($\sim 65$ mmHg), which develops significantly more severe GS within 6 wk (3, 4, 22, 38, 52, 68).

The slow development of GS, despite an abundance of hemodynamic and nonhemodynamic mechanisms that promote GS, indicates that there must be factors associated with the STZ-diabetes model in vivo that retard GS, although none has as yet been definitively identified. The spontaneously reduced ambient BP load documented by chronic BP radiotelemetry, instead of the previously reported high normal to moderately increased tail-cuff BP (140–160 mmHg) in this STZ-diabetes model (4, 60, 68, 69), may represent one such potential mechanism (vide infra). Although the precise reasons remain to be established, the low BP does not seem to be due to plasma volume depletion (39). Measurements of plasma volume in similarly partially insulin-treated STZ-diabetic rats have shown the absolute values not to be different from controls but in fact increased when corrected for body weight (39). The elevated atrial natriuretic peptide levels and the suppressed peripheral plasma renin levels that have been reported in these rats are consistent with such relative plasma volume expansion (4, 20, 48, 58). Consistent with such interpretations, the significant lower heart rate in the STZ-diabetic rats compared with control and RMR rats also does not support the presence of a significant plasma volume deficit. Thus it is more likely that the reduced BP in STZ-diabetes may result from a shift of the pressure natriuresis curve to the left by the characteristic diabetic renal vasodilatation, just as renal vasoconstrictors shift the pressure natriuresis curve to the right (35).

Regardless of the underlying mechanisms, given that even moderate hypertension accelerates and antihypertensive therapy retards the progression of both clinical and experimental diabetic and nondiabetic nephropathies (4, 6, 9–11, 28, 32, 41, 52, 57), a spontaneously lower ambient BP clearly has the potential to contribute to the slow development of overt nephropathy in this STZ-diabetes model. Even though the impact of superimposed pharmacological hypertension was not directly examined in the present studies because of concerns regarding the direct BP-independent deleterious effects of such agents, substantial evidence supports the importance of BP as a determinant of GS in this model. GS is accelerated when corrected for body weight (39). The elevated atrial natriuretic peptide levels and the suppressed peripheral plasma renin levels that have been reported in these rats are consistent with such relative plasma volume expansion (4, 20, 48, 58). Consistent with such interpretations, the significant lower heart rate in the STZ-diabetic rats compared with control and RMR rats also does not support the presence of a significant plasma volume deficit. Thus it is more likely that the reduced BP in STZ-diabetes may result from a shift of the pressure natriuresis curve to the left by the characteristic diabetic renal vasodilatation, just as renal vasoconstrictors shift the pressure natriuresis curve to the right (35).

Such data additionally indicate that not only may the beneficial effects of a reduced BP reflect an absence of the direct adverse effects of hypertension but reduced BP may also dampen the deleterious signal transduction pathways of other nonhemodynamic mechanisms. The development of significant mesangial matrix expansion in STZ-diabetic rats but its very slow progression to GS in the present study is consistent with such interpretations. Although such effects have not been directly investigated, there is other indirect evidence to support their existence. For instance, there is extensive in vitro evidence for the direct BP-independent tissue-damaging effects of angiotensin II and aldosterone (25, 26, 42, 66). However, little evidence of the activation of these deleterious pathways in vivo is observed in the absence of elevated pressures despite substantial angiotensin and aldosterone increases during low salt intake, congestive heart failure, or cirrhosis or in the clipped kidney of the two kidney-one clip model (10). Nevertheless, the fact that the STZ-diabetic rats in the present study developed proteinuria and GS comparable to those observed in control rats despite a significantly lower BP suggests that such reduced pressures may not completely block the nonhemodynamic pathways. Comparable BP reductions in normal rats, at least with angiotensin-converting enzyme inhibitors, have been shown to significantly retard the development of proteinuria and GS that is seen with aging in most rat strains (5, 52). That the diabetic milieu contributes to the pathogenesis of GS through distinct additional, but likely interacting, mechanisms with those operative after uncomplicated RMR (21, 34, 56, 61) is also suggested by the accelerated development of GS when UNX is combined with partially treated STZ-diabetes (2).

In any event, if the above interpretations regarding the potentially protective effects of a reduced BP load on diabetic pathogenetic mechanisms are valid, they may also provide a partial explanation for the long delay (15 yr) in the development of overt nephropathy in Type 1 juvenile diabetic patients with lower absolute BP, despite the early onset of renal hypertrophy, hyperfiltration, and presumably other nonhemodynamic mechanisms (56, 64). And, indeed, 24-h ambulatory BP monitoring in such patients has revealed modest increases in BP load, due to a loss of nocturnal dip, to precede the development of overt nephropathy (47). Once nephropathy is initiated, it may not only contribute to further BP increases but also enhance the glomerular transmission of the elevated pressures due to the renal autoregulatory impairment that seems to develop concurrently (17). Such enhanced glomerular BP transmission likely results in the acceleration of the nonhemodynamic and metabolic pathways for diabetic GS as suggested by the data from the two kidney-one clip model (50). The initiation of such a vicious pathogenetic cycle probably accounts for the rapid downhill renal course in these patients once overt nephropathy has developed (40, 56). Such interpretations are also supported by the extensive epidemiological and clinical trial data that have demonstrated the marked adverse effects of even modest BP elevations on diabetic target organ damage including nephropathy and that have led to the progressive lowering of the “optimal BP goals” for these patients (6, 40, 41, 65).

However, given the substantially elevated $P_{\text{GC}}$ reported in this STZ-diabetes model, such interpretations are seemingly at odds with the current concepts that both the adverse effects of elevated BP and the beneficial effects of BP reductions are
mediated though parallel changes in $P_{GC}$ (3, 4, 10, 23, 29, 31, 38, 52, 68). However, isolated $P_{GC}$ measurements may not accurately reflect the fluctuating ambient $P_{GC}$ profiles resulting from BP lability in states of enhanced glomerular pressure transmission (10, 11, 30, 32). Additionally, such $P_{GC}$ measurements may also be compromised by surgery and anesthesia-induced renal release and neurohormonal activation (10, 11, 13). Such limitations may in fact account for the poor correlation that has sometimes been observed between $P_{GC}$ and GS (25, 26), even in models that demonstrate an excellent correlation between radiotelemetrically measured BP and GS (9, 13, 29, 30). Moreover, if these $P_{GC}$ values are accepted as being truly representative of the ambient $P_{GC}$ in STZ-diabetes, the 5/6 renal ablation, and the UNX models, the inference would be inescapable that the diabetic milieu somehow protected against the adverse effects of glomerular capillary hypertension, given that the development of GS in STZ-diabetes is significantly slower and $P_{GC}$ significantly higher than those in UNX rats (4, 22, 36, 68). In fact, it is more likely that such $P_{GC}$ of $\sim$60 mmHg under anesthesia may not truly reflect the ambient $P_{GC}$ in STZ-diabetic rats with conscious mean arterial pressures of only 90–95 mmHg that are substantially lower than the mean arterial pressures of 110–120 mmHg at which such $P_{GC}$ measurements have been obtained, usually after administration of plasma and/or albumin solutions to restore surgical losses (2, 4, 39, 49, 68, 69). Alternatively, such differences may reflect strain differences between Sprague-Dawley and Munich-Wistar rats (49, 54), because elevated $P_{GC}$ values have been observed in the Wistar-Kyoto rat and SHR with partially treated STZ-diabetes but not in the Sprague-Dawley or Wistar rats despite the presence of significant hyperfiltration (54). However, regardless of the $P_{GC}$ measurements, the very slow development of overt GS despite hyperfiltration is common to STZ-diabetes in all normotensive rat strains.

Such interpretations also do not exclude the contributions of other BP-independent mechanisms including species (genetic) differences to the observed resistance to overt nephropathy in this diabetic model (24, 36, 49, 54, 56, 64). The importance of genetic factors in the susceptibility to diabetic nephropathy is strongly supported by both clinical data (44) and the recent observations examining such susceptibility in various strains of mice, although adequate BP data are not available for these studies (15, 70). In this context, it is also of note that the segmental GS lesion, which is the dominant lesion that is eventually observed in partially insulin-treated rodent STZ-diabetes, even when its development is accelerated by UNX or coexistent hypertension, is not a notable feature of human diabetic nephropathy (2, 18, 19, 24, 49, 50, 56, 64), although glomerular basement membrane thickening and glomerular hypertrophy are observed in both (24, 36, 56, 74). Also of interest, it is the untreated severely diabetic rat that seems to develop at least an early form of the diffuse diabetic GS with disproportionate mesangial expansion and a loss of glomerular capillary surface area (24, 36, 49, 56, 74). However, such rats do not exhibit hyperfiltration and may in fact have a reduced glomerular filtration rate (24, 39, 49, 54, 56, 64). Thus both the untreated and partially treated STZ-diabetic rats exhibit only partial resemblance to the human diabetic nephropathy phenotype. However, while genetic differences may explain some of the differences in the glomerular lesion phenotype, they cannot explain the resistance to segmental GS in STZ-diabetes, as the rat readily develops these lesions in many diverse settings including aging (5, 52, 57). On the other hand, such resistance is more plausibly explained, at least in part, by the reduced BP in the rat STZ-diabetes model. Such data also underscore the need for accurate BP phenotyping for valid interpretations during investigations of susceptibility to diabetic nephropathy in experimental models.

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