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Glomerular hemodynamics in experimental diabetes mellitus

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Glomerular hemodynamics in experimental diabetes mellitus. Micropuncture studies were performed in three groups of euvolemic male Munich-Wistar rats: 8 control rats, 7 severely hyperglycemic rats made diabetic with streptozotocin (60 mg/kg, i.v.), and 6 moderately hyperglycemic rats made diabetic by the same method but given 2 U of NPH insulin daily. Glucose concentrations at the time of micropuncture study averaged 115 ± (SEM) 10, 565 ± 12, and 375 ± 23 mg/dl, respectively. Single nephron GFR (SNGFR) values were significantly lower (28.8 ± 1.9 nl/min) in severely hyperglycemic rats than they were in controls (48.9 ± 3.8). This reduction in SNGFR was due mainly to a fall in glomerular plasma flow rate (Q_A). In contrast, moderately hyperglycemic rats exhibited glomerular hyperfiltration, with SNGFR values averaging 69.0 ± 8.0 nl/min. This hyperfiltration resulted from elevations in values for Q_A and glomerular transcapillary hydraulic pressure difference ($\Delta\bar{P}$) to levels significantly above control. These alterations in SNGFR in severely hyperglycemic and moderately hyperglycemic rats, relative to controls, were paralleled by changes in whole kidney GFR and mimic the changes in GFR observed in diabetic patients with analogous degrees of hyperglycemia. Measurements of blood volumes in separate groups of control, severely, and moderately hyperglycemic rats revealed equivalent absolute blood volumes in all three conditions and increased blood volumes, relative to body weight, in both groups of hyperglycemic rats. Thus, SNGFR is increased in diabetic rats with moderate hyperglycemia but decreased in those with severe hyperglycemia, and these changes are not simply related to variations in circulating blood volume.

Hémodynamique glomérulaire dans le diabète sucré expérimental. Des microponctions ont été réalisées dans trois groupes de rats Munich-Wistar euvolémiques: 8 rats contrôles, 7 rats très hyperglycémiques atteints de diabète déterminé par la streptozotocyne (60 mg/kg, i.v.), et 6 rats modérément hyperglycémiques rendus diabétiques par la même méthode mais qui recevaient deux unités d'insuline NPH par jour. Les concentrations de glucose au moment des microponctions étaient en moyenne de 115 ± (SEM) 10, 565 ± 12, et 375 ± 23 mg/dl, respectivement. Les valeurs de débits de filtration glomérulaire individuels (SNGFR) étaient significativement inférieures (28,8 ± 1,9 nl/min) chez les rats sévèrement hyperglycémiques par rapport aux contrôles (48,9 ± 3,8). Cette réduction de SNGFR était surtout due à une chute du débit plasmatique glomérulaire (Q_A). Au contraire, les rats modérément hyperglycémiques avaient une hyperfiltration glomérulaire avec des valeurs en moyenne de 69,0 ± 8,0 nl/min. Cette hyperfiltration était la conséquence de valeurs de Q_A et de la différence de pression hydraulique transcapillaire glomérulaire ($\Delta\bar{P}$) à des niveaux significativement supérieurs aux contrôles. Ces modifications de SNGFR chez les rats sévèrement et modérément hyperglycémiques, par rapport aux contrôles, étaient reflétées par des modifications du débit de filtration glomérulaire, GFR, et reproduisent les modifications de GFR observées chez ces malades diabétiques ayant des degrés semblables d'hyperglycémie. La mesure du volume sanguin dans des groupes contrôles différents, sévèrement et modérément hyperglycémiques, a montré des volumes absolus équivalents dans les trois situations et des volumes augmentés par rapport au poids corporel dans les deux groupes de rats hyperglycémiques. Ainsi SNGFR est augmenté chez les rats diabétiques modérément hyperglycémiques, mais diminué chez ceux qui sont sévèrement hyperglycémiques et ces modifications ne sont pas seulement en rapport avec des variations du volume sanguin circulant.

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Several lines of evidence indicate that renal hemodynamics are altered in clinical and experimental diabetes mellitus, and that changes in renal hemodynamics play a role in the pathogenesis of the nephropathy commonly seen in this metabolic disorder [1–5]. For example, the renal lesion that develops in diabetic rats may be hastened in its progression by prior unilateral nephrectomy or exposure to two-kidney Goldblatt hypertension [4, 5]. Moreover, numerous studies have documented a consistent increase in glomerular filtration rate (GFR) in early juvenile onset diabetes during periods of poor metabolic control [1]. Conversely, when hyperglycemia is more severe, as in diabetic keto-acidosis, hyperfiltration no longer occurs [2]. Thus, because of the potential importance of alterations in renal microcirculatory dynamics to these functional responses of the glomerulus in diabetes, we investigated the hemodynamic determinants of GFR at a relatively early stage of experimental diabetes induced in Munich-Wistar rats.

Methods

Micropuncture studies were performed on 21 adult male Munich-Wistar rats, each weighing 185

to 315 g and having free access to water and a standard rat pellet diet. Three groups of rats were studied: *control,* 8 normal rats; *severe hyperglycemia,* 7 rats given streptozotocin (60 mg/kg, i.v.) in citrate buffer; *moderate hyperglycemia,* 6 rats made diabetic in the same fashion but given 2 U of NPH insulin s.c. each evening for at least 3 weeks prior to study. Diabetic rats were studied 2 to 15 weeks after streptozotocin administration (mean, 74 ± 9 days). All diabetic animals were glycosuric. By semiquantitative testing (Multistix®, Ames Company), severely hyperglycemic rats demonstrated 3 to 4+ urine glucose; and moderately hyperglycemic animals, 1 to 2+.

On the morning of micropuncture study, rats were anesthetized with Inactin® (100 mg/kg body weight, i.p.). They were prepared in standard fashion for micropuncture [6] and given isoncotic rat plasma equal to 1% of body wt i.v. to replace surgical losses [7]. Normal rats received plasma obtained from nondiabetic donors, and diabetic rats received plasma from diabetic donors. Plasma glucose concentration was measured at the beginning of each micropuncture experiment, using a Beckman glucose analyzer (model 2, Beckman Instruments, Inc., Fullerton, California). Samples of proximal tubular fluid were obtained by micropuncture for determination of flow rate and inulin concentration by the method of Vurek and Pegram [8]. Samples of tubular fluid obtained from 2 diabetic animals prior to inulin administration showed fluorescence equal to the blank, indicating that there is no interference with this assay by some substance(s) peculiar to the diabetic state. Efferent arteriolar blood samples were obtained by measurement of total protein concentration [9]. Hydraulic pressure measurements were made in cortical tubules and vessels by the servo-null micropipette technique [6]. The details of the calculations used are given elsewhere [6].

In a separate group of 17 rats, measurements of blood volume were made by the method of Sterling and Gray [10] with ^{51}Cr-labeled rat red blood cells. Rats were studied under the same three metabolic conditions as described above. These rats were studied after 4 to 6 weeks of diabetes and 3 to 5 weeks of insulin administration. Statistical analyses were performed by the paired or unpaired Student's *t* test as appropriate. Statistical significance was defined as $P < 0.05$.

Results

Plasma glucose concentrations at the time of micropuncture averaged 115 ± 10, 565 ± 12, and 375 ± 23 mg/dl (means ± SEM) in normal, severely, and moderately hyperglycemic rats, respectively. Rats with severe hyperglycemia had significantly lower body weights than either control ($P < 0.05$) or moderately hyperglycemic rats ($P < 0.005$), but the latter two groups demonstrated no statistically significant difference in body weight. Mean values for whole kidney GFR, femoral arterial pressure ($\overline{AP}$), SNGFR, and determinants of SNGFR are summarized in Table 1. Whole kidney GFR averaged 1.10 ± 0.06 in control rats and 0.76 ± 0.03 ml/min in the severely hyperglycemic group. Values for SNGFR paralleled this whole kidney GFR trend, averaging 48.9 ± 3.8 and 28.8 ± 1.9 nl/min in control and severely hyperglycemic groups, respectively. On average, the mean transmembrane hydraulic pressure difference ($\overline{\Delta P}$) did not differ significantly between the groups and thus did not account for the measured differences in GFR and SNGFR. Similarly, there were no statistically significant differences in afferent arteriolar protein concentrations (C_A) between these groups.

The glomerular ultrafiltration coefficient (K_f) was lower, on average, in severely hyperglycemic rats than it was in controls (Table 1). This difference potentially accounts for a portion of the lower SNGFR in the severely hyperglycemic group. Because both control and severely hyperglycemic rats were, however, in filtration pressure equilibrium, with no statistical difference between efferent arteriolar colloid osmotic pressure (Π_E) and $\overline{\Delta P}$ in either group ($P > 0.2$), only minimal values for K_f may be calculated. Thus, it is not possible to state with certainty that the lower average minimum is truly less than the higher. In any case, the lower value for SNGFR in the severely hyperglycemic group can be largely explained by the lower values for initial glomerular plasma flow rate (Q_A) in the severely hyperglycemic group, averaging 86 ± 8 nl/min compared with 142 ± 11 nl/min ($P < 0.05$) in controls.

Moderately hyperglycemic rats showed important differences from the above in their pattern of glomerular hemodynamics. In this group, both whole kidney GFR and SNGFR averaged significantly higher than they did in control or severely hyperglycemic animals (1.47 ± 0.13 ml/min and 69 ± 8 nl/min). But, GFR per gram of kidney weight was not different in this group from control values due to the increase in kidney weight in moderately hyperglycemic rats. The hyperfiltration could be attributed to two factors. First, Q_A was increased to 240 ± 34 nl/min, a value significantly higher than in either of the other groups studied (Table 1). Second,

Table 1. Summary of in vivo microcirculation studies in control, severely hyperglycemic and moderately hyperglycemic rats[a]

	Body wt *g*	Kidney wt *g*	Plasma glucose *mg/dl*	Hct *vol %*	$\overline{AP}$	$\bar{P}_{GC}$	P_T	$\overline{\Delta P}$	P_E
					mm Hg				
Control ($N = 8$)	247 ±11	1.14 ±0.06	115 ±10	45 ±1	103 ±4	47.5 ±1.2	12.3 ±0.2	35.2 ±1.3	17.6 ±0.4
Severe hyperglycemia ($N = 7$)	221 ±8	1.27 ±0.06	565 ±12	45 ±1	102 ±4	47.7 ±1.5	11.2 ±0.3	36.6 ±1.5	17.2 ±0.8
Moderate hyperglycemia ($N = 6$)	272 ±13	1.49 ±0.06	375 ±23	45 ±1	114 ±5	56.4 ±1.9	12.0 ±0.6	44.4 ±1.6	17.6 ±1.0
P, control vs. severe hyperglycemia	<0.05	NS	<0.001	NS	NS	NS	<0.005	NS	NS
P, severe hyperglycemia vs. moderate hyperglycemia	<0.005	<0.05	<0.001	NS	NS	<0.005	NS	<0.005	NS
P, control vs. moderate hyperglycemia	NS	<0.02	<0.001	NS	NS	<0.005	NS	<0.005	NS

[a] Values are the means ± SEM. Abbreviations are defined as follows: $\overline{AP}$, mean femoral arterial pressure; $\bar{P}_{GC}$, mean glomerular capillary hydraulic pressure; P_T, proximal tubular hydraulic pressure; $\overline{\Delta P}$, mean transmembrane hydraulic pressure difference ($P_{GC} - P_T$); P_E, efferent arteriolar hydraulic pressure; C_A and C_E, afferent and efferent arteriolar protein concentration; $\Pi_A$and Π_E, afferent and efferent arteriolar colloid osmotic pressure; SNFF, single nephron filtration fraction; SNGFR, single nephron glomerular filtration rate; Q_A, initial glomerular plasma flow rate; R_A, R_E, and R_T, afferent, efferent, and total arteriolar resistance to blood flow; K_f, glomerular ultrafiltration coefficient.

the mean value of $\overline{\Delta P}$ was also significantly higher, due solely to a higher mean value for glomerular capillary hydraulic pressure ($\bar{P}_{GC}$). Because the moderately hyperglycemic rats were in filtration pressure disequilibrium with Π_E less than $\overline{\Delta P}$ ($P < 0.01$), unique values for K_f were calculable. On average, the unique K_f was not significantly different from the mean minimal value in the control group and thus could not account for the higher SNGFR with moderate hyperglycemia. Likewise, the slightly higher values for C_A and Π_A in the moderately hyperglycemic group would oppose filtration and thus do not account for the increased SNGFR in this group.

Calculated afferent and efferent arteriolar and total arteriolar resistances are summarized in Table 1. The two groups of diabetic rats have contrasting patterns of microvascular resistances. The severely hyperglycemic animals demonstrated increases in both afferent and efferent resistances as well as total arteriolar resistance when compared with normal rats. But, the moderately hyperglycemic group had lower afferent and total resistances than did the normal controls, whereas the numerically lower mean value of efferent arteriolar resistance, R_E, was not statistically different from the control value. Thus, there was a tendency for intrarenal vasoconstriction in the severely hyperglycemic group but an opposite tendency to vasodilatation in the moderately hyperglycemic group.

Measurements of blood volume in a separate group of 17 rats demonstrated equivalent absolute blood volumes in these three metabolic states, with values averaging 13.7 ± 1.0, 13.9 ± 0.6, and 15.7 ± 1.0 ml/rat in normal, severely, and moderately hyperglycemic rats, respectively. These absolute values did not differ from one another statistically. When factored by mean body weight, however, blood volumes averaged 4.2 ± 0.2, 5.8 ± 0.3, and 5.5 ± 0.4 ml per 100 g in the same three groups, with the latter two values being significantly higher ($P < 0.05$) than control but not significantly different from one another.

Discussion

In severely hyperglycemic diabetic rats, SNGFR and GFR values fell below control levels because of the lower mean value for glomerular plasma flow rate (Q_A). With moderate hyperglycemia, achieved by chronic low dose insulin administration, hyperfiltration occurred due to elevations of both Q_A and $\overline{\Delta P}$. Of note, these changes in glomerular dynamics occurred at a stage in this experimental model of diabetes when glomerular structural lesions have been shown to be absent [13].

These findings are therefore in keeping with the clinical observation that GFR tends to be reduced in patients with severe uncontrolled hyperglycemia (diabetic keto-acidosis or hyperglycemic nonketotic coma), whereas hyperfiltration is usually found in human diabetics when blood glucose concentrations are elevated to a lesser degree [1, 2]. The reversible decline in GFR seen in patients with diabetic keto-acidosis is usually accompanied by a fall in

Table 1. (*continued*)

C_A	C_E	Π_A	Π_E	SNFF	SNGFR	GFR	GFR/g kidney	Q_A	R_A	R_E	R_T	K_f
g/dl		*mm Hg*			*nl/min*	*ml/min*	*ml/min/g*	*nl/min*	$\times 10^{10}$ *dynes · sec · cm*$^{-5}$			*nl/(sec · mm Hg)*
5.4	8.3	17.6	33.6	0.35	48.9	1.10	0.97	142	3.0	2.1	5.0	>0.095
±0.3	±0.1	±0.4	±0.9	±0.01	±3.8	±0.06	±0.05	±11	±0.3	±0.2	±0.4	±0.013
5.2	8.1	15.4	32.2	0.35	28.8	0.76	0.61	86	4.7	3.5	8.4	>0.048
±0.2	±0.4	±1.7	±2.5	±0.02	±1.9	±0.03	±0.05	±8	±0.6	±0.2	±0.8	±0.010
6.0	8.5	20.2	35.1	0.30	69.0	1.47	0.99	240	1.9	1.6	3.5	0.080
±0.2	±0.1	±0.9	±1.0	±0.02	±8.0	±0.13	±0.08	±34	±0.3	±0.3	±0.7	±0.015
NS	NS	NS	NS	NS	<0.001	<0.001	<0.001	<0.005	<0.025	<0.001	<0.005	
<0.02	NS	<0.02	NS	NS	<0.001	<0.001	<0.005	<0.005	<0.005	<0.001	<0.001	
<0.02	NS	<0.02	NS	NS	<0.05	<0.02	NS	<0.01	<0.01	NS	<0.05	NS

renal plasma flow and depletion of extracellular fluid volume [2, 14]. With lesser degrees of hyperglycemia, however, extracellular volume tends to expand, rather than contract, presumably because the associated glycosuria and osmotic diuresis are less profound than they are with severe hyperglycemia [15]. It has been suggested that these changes in extracellular fluid volume underlie, at least in part, the patterns of hyperfiltration and reduced filtration seen in these two groups of diabetic human subjects [15].

Not all investigators have found an increase in plasma volume in moderately hyperglycemic diabetics when compared with normal subjects [16]. Further, elevation of blood glucose levels achieved by glucose loading in normal subjects has led to an increase in GFR but not of the same degree as comparable hyperglycemia in diabetics. This implies that factors in addition to glucose level (and thereby changes in plasma volume) may effect the changes in GFR [15]. The results of blood volume measurements in the present study suggest that neither absolute nor relative blood volume contraction alone may be invoked as the cause for the reduced GFR and SNGFR in the severely hyperglycemic rats. Indeed both groups of hyperglycemic rats had significantly greater blood volumes per unit of body weight than did controls, whereas SNGFR was reduced in severely hyperglycemic rats but increased in rats with more moderate hyperglycemia. The tendency for increased plasma volume has also been demonstrated in alloxan diabetic rats with a mean blood glucose of 616 mg/dl [12]. Thus, the differences in SNGFR in our two groups of diabetic rats appear not to be a simple consequence of differences in circulating blood volume. More insight is gained, however, when these changes in volume are considered in the context of the intrarenal microvascular resistances that characterize each of the hyperglycemic groups in the present study. Thus, the high relative blood volume, together with the low values for R_A and R_E, made possible the striking elevations in Q_A and SNGFR measured in the moderately hyperglycemic group. By contrast, despite equivalent elevations in relative blood volume in the severely hyperglycemic group, marked increases in R_A and R_E were present. Therefore, Q_A and SNGFR were lower than control in this group. In other words, despite the relative blood volume expansion in the severely hyperglycemic group, intense renal vasoconstriction prevented the increases in Q_A and SNGFR seen with more moderate hyperglycemia.

Studies of clinical and experimental diabetes have demonstrated that renal size increases early in this condition, and the increased size is by some unknown mechanism related to the degree of metabolic control and can be reversed with rigorous insulin therapy [1, 17]. Glomerular dimensions also change relatively early in experimental diabetes [18]. Thus, it is possible that the greater weight of the kidneys in the moderately hyperglycemic group may account in part for the greater filtration rates. The finding that GFR per gram of kidney weight did not increase in the moderately hyperglycemic animals is consistent with such a possibility. But changes in kidney weight alone do not explain all the results because severely hyperglycemic rats had kidney weights that were not statistically significantly different from normal animals, yet these animals nevertheless demonstrated lower than normal filtration rates.

An increase in glomerular capillary surface area has been estimated from morphometric analyses of renal biopsy specimens in diabetic subjects, and this increased surface area has also been proposed to account for the hyperfiltration observed in diabetic subjects [1, 18]. Even if similar increases in glomerular capillary surface area were present in our rats, this would fail to account for measured differences in GFR and SNGFR between severely and moderately hyperglycemic animals because K_f values were not altered to an important physiologic extent in either group. Rather, the finding in moderately hyperglycemic rats of elevations in Q_A and $\overline{\Delta P}$ more readily account for the observed increments in GFR and SNGFR in this group, whereas in severely hyperglycemic rats the decline in Q_A constitutes the main factor responsible for the measured falls in SNGFR and GFR.

It is possible that one or more hormonal systems are responsible for the observed resetting of the glomerular pressures and flows in diabetic rats. Glucagon and growth hormone are both present in increased concentrations in the plasma of poorly controlled diabetic subjects, and both hormones are capable of increasing GFR [20–23]. Insulin may also play a role in that this hormone has been shown to reduce GFR acutely in uncontrolled diabetics and to be capable of binding to specific receptors in isolated glomeruli [22, 24, 25]. In this regard, it is possible that the low dose of insulin used to produce moderate hyperglycemia may have altered the glomerular hemodynamics by some means independent of its effect on blood glucose. Of note, the diabetic state has also been shown to be associated with alterations in vascular responsiveness to such potent vasoactive substances as angiotensin II and catecholamines, humoral agents capable of initiating profound alterations in glomerular microcirculatory dynamics [12, 26, 27]. Similarly, prostaglandins and other endogenous vasodilators have been shown to exert dramatic influences on glomerular hemodynamics [6]. Of interest are the findings that prostaglandin production is increased in platelets of diabetic patients and that the renal medulla exposed to varying glucose concentrations in vitro alters its production of these local vasodilators [28, 29]. Additional studies are therefore required to ascertain whether these or other humoral agents are responsible for the striking alterations in glomerular hemodynamics observed in diabetic rats. Likewise, whether chronic modifications of these humoral responses influence the onset and progression of the structural damage known to underlie the nephropathy that develops in this common metabolic disorder in man remains an important issue to resolve.

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