Diabetologia (1981) 21: 409–414

Diabetologia

Renal Function in Streptozotocin-Diabetic Rats

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Summary. Renal function was examined with micropuncture methods in the insulin-treated streptozotocin-diabetic rat. Kidney glomerular filtration rate was significantly higher in the diabetic rats (1.21 ml/min) than in the control group (0.84 ml/min) Nephron glomerular filtration rate increased in proportion to the rise in kidney glomerular filtration rate (diabetic rats: 37.0 nl/min; control rats: 27.9 nl/min). Likewise renal plasma flow was significantly higher in the diabetic rats (4.1 ml/min) than in the control group (3.0 ml/min). Glomerular capillary pressure was identical in both groups (56.0 and 56.0 mmHg, respectively). The proximal intratubular pressure was significantly reduced in the diabetic rats (10.4 mmHg; control value: 12.5 mmHg). The effective glomerular ultrafiltration coefficient was slightly but not significantly higher in the diabetic rats (0.027 nl $s^{-1}mmHg^{-1}$) than in the control group (0.023 nl $s^{-1}mmHg^{-1}$). Kidney weight was significantly higher in the diabetic rats (1.15 g; control rats: 0.96 g) while body weight was similar in both groups (diabetic rats: 232 g; control rats: 238 g). Calculations indicate that the increases in transglomerular hydraulic pressure, renal plasma flow and ultrafiltration coefficient of the glomerular membrane contribute about equally to the rise in glomerular filtration rate. The increases in the values of the determinants of glomerular filtration rate may be the result of renal hypertrophy. These studies suggest that this model provides a useful method for investigating kidney function in diabetes, which may have relevance for our understanding of the kidney abnormalities in human diabetes.

Key words: Streptozotocin, diabetes, rat, micropuncture, renal plasma flow, glomerular filtration, hydraulic pressure, ultrafiltration coefficient.

Glomerular filtration rate (GFR) is increased in short-term insulin-dependent diabetes mellitus [7, 12, 20]. The rise in GFR is associated with an increase in kidney size [7, 21]. GFR is determined by the product of the effective ultrafiltration coefficient of the glomerular membrane and the mean transglomerular ultrafiltration pressure. Accordingly, the rise in GFR associated with an increase in kidney size must be caused by changes in these determinants of GFR [6]. The present experiments were carried out to study the contribution of these determinants of GFR to the rise in filtration rate observed in streptozotocin diabetic rats.

Materials and Methods

Male Wistar rats weighing between 140 and 190 g were randomly allocated into an experimental and a control group. The animals were kept in metabolic cages with free access to tap water and commercial food ad libitum (Rostock rat pellets, 0.5% w/w NaCl, Korn & Foderstofkompagniet, Aarhus). Body weight, urine volume and the concentrations of glucose (Testape, Lilly) and ketone bodies (Ketostix, Ames) were recorded daily. Blood glucose (Reflomat Boehringer-Mannheim) was measured at 1200 h three times a week.

The rats in the experimental group were given streptozotocin (70 mg/kg body weight IV). Within 48 h after the injection all animals were diabetic with blood glucose values above 10 mmol/l, glycosuria and ketonuria. Insulin treatment was given daily in order to avoid ketonuria and to ensure weight gain but without attempting to attain strict metabolic control. Very long-acting highly-purified bovine insulin, pH 5.5 (Ultralente MC, Novo) [25] was administered SC from 2 days after the induction of the diabetes, beginnig with 4 U on day 1 and 2 U on day 2 of treatment. The treatment was continued with a mean dose of 0.4 U/day (range 0.2–1.0 U/ day).The control group received sham injections of saline instead of streptozotocin and insulin.

Experiments were carried out between 7 and 27 days after induction of diabetes. The rats were anaesthetized by Inactin (5-aethyl-5-(1′-methyl-propyl)-2-barbiturate, 120 mg/kg of body weight IP), placed on a heating pad and transferred to the micropuncture laboratory. Preparation of the animals and surgical

0012-186X/81/0021/0409/$01.20

procedures were as described previously [30]. Briefly, the left kidney was exposed through a subcostal incision. The kidney was dissected free of the surrounding structures, placed in a lucite kidney cup and superfused by mineral oil maintained at 37.5 °C to prevent the surface from drying [30]. All rats received 2 ml of 0.9% saline IV to replace fluid losses during surgery. This was followed by a maintenance infusion of 0.9% saline administered at 1.2 ml/h to the control rats. Diabetic rats with preoperative urine flow rates above and below 50 ml/day were given 0.9% saline, 3.2 and 2.4 ml/h respectively. After the preparation of the kidney, inulin-^{14}C-carboxylic acid was added to the infusion solution to deliver 50 μCi/h. A 1-h equilibration period was allowed before tubular fluid collections were begun.

To measure kidney GFR, both in the left kidney subjected to micropuncture and in the untouched right kidney, catheters were placed in the left ureter and in the bladder respectively. Timed collections of urine were made under mineral oil in preweighed vials. Arterial blood samples of about 75 μl were taken from the femoral artery catheter. Two hours after commencing micropuncture experiments a blood sample was obtained by puncturing the renal vein with a glass pipette having a tip diameter of 50 μm [1].

To measure nephron GFR an early segment of a proximal convoluted tubule was punctured by a pressure measuring pipette of the Landis type [17]. An oil-filled collection pipette was then inserted at the distal extreme of the same proximal tubule [30]. A short oil block was introduced and a timed collection of tubular fluid was obtained at the pre existing free flow pressure.

Hydraulic pressures at the end of the efferent arterioles and in distal tubules were measured using a servo-nulling pressure measuring device (Model 4, Instrumentation for Physiology and Medicine, San Diego, CA) [17].

To measure the glomerular capillary pressure [13] the stop-flow pressure in the same proximal tubule was recorded after completing a collection. To obstruct the flow of tubular fluid the previously injected oil block was enlarged after the insertion of a second oil-filled micropipette. The most proximal segment was then punctured by a servo-nulling pressure pipette [17]. The Landis pipette was withdrawn and the oil block extended back to the servo-nulling pipette. The early stop-flow pressure was recorded when the oil meniscus had been maintained in this position for about 1 min [13]. To confirm that the puncture site was in the most proximal segment obtainable, excess oil was then injected.

To validate the stop-flow method, direct measurements of glomerular capillary pressure were made in a 4 mm^2 corticotomy [32] made after the clearance experiments. The capillary pressures were measured in two to four glomeruli using 2 μm servo-nulling pipettes filled with 1% lissamin green in NaCl, 1.0 mmol/l. The criteria for acceptance were as described by Tonder and Aukland [32]. For comparison stop-flow pressures were obtained in intact surface nephrons adjacent to the corticotomy.

At the end of the experiments the kidney weight was determined after allowing the intrarenal blood to drain away. The tubular fluid samples were treated as described previously [30]. Plasma inulin activities were corrected by refractometry for the content of solids in plasma [1]. The plasma protein concentration was measured by the Lowry method with a coefficient of variation of 3%. The colloid osmotic pressure of plasma was calculated from the protein concentration, C (g/l), using the expression [10]:

$$\pi(C) = 0.1631\,C + 0.00294\,C^2.$$

Kidney GFR was calculated from the urine to plasma inulin ratio, U/P_{inulin}, and the urine flow rate, $\dot{V}_u$, as follows:

$$GFR = U/P_{inulin} \times \dot{V}_u$$

The filtration fraction of the whole kidney, FF, was calculated from the plasma inulin concentrations in the femoral artery, CA, in the renal vein, CV, and in the urine, CU, using the expression [1]:

$$FF = CU/(CU-CV) \times (CA-CV)/CA$$

Renal plasma flow, RPF, was calculated from kidney GFR and the filtration fraction as follows:

$$RPF = GFR/FF$$

Nephron GFR was calculated from the tubular fluid to plasma inulin ratio, TF/P_{inulin}, and the volume of tubular fluid collected per minute, $\dot{V}$, using the expression:

$$\text{Nephron GFR} = TF/P_{inulin} \times \dot{V}$$

The rate of fluid reabsorption in the proximal tubule was calculated as follows:

$$\text{Nephron GFR} - \dot{V}$$

The glomerular capillary pressure was calculated as the sum of the stop flow pressure and the colloid osmotic pressure calculated from the protein concentration in the femoral artery [10, 13].

The effective glomerular capillary filtration coefficient was calculated using a mathematical model of glomerular ultrafiltration [10] with the assumptions that there is no hydraulic pressure gradient along the glomerular capillaries and that the filtration fraction of the superficial nephrons is equal to that of the whole kidney. These assumptions have been found valid in the hydropenic rat [4, 8].

Statistical analysis was made with Wilcoxon's rank sum test for results obtained by more than one measurement in each rat, whilst Student's t-test was used for results derived from a single measurement in each rat. Probabilities below 5% were considered statistically significant.

Results

Between one and six measurements were made in each rat. Table 1 shows the mean values and the coefficients of variation for the individual rats in parentheses. The results from the diabetic and the control groups of rats are given as the mean ± standard error of the mean (SEM) values for the individual rats. The results are based on eight experiments in each group unless stated otherwise.

Pressure Measurements

The mean arterial pressure in diabetic animals was 105 ± 3 mmHg which is not significantly different from the value of 107 ± 4 mmHg in control rats. The early proximal stop-flow pressure was 39.7 ± 0.7 mmHg in diabetics which is similar to 38.9 ± 0.4 mmHg in controls. The calculated values of glomerular capillary pressure were the same in the two groups: 56.0 ± 0.6 mmHg in diabetics and 56.0 ± 0.9 mmHg in controls. The hydraulic pressures at

Table 1. Mean values of left kidney function for individual rats

	Blood glucose (mmol/l)	Kidney weight (g)	Glomerular filtration rate (ml/min)	Filtration fraction	Renal plasma flow rate (ml/min)	Nephron glomerular filtration rate (nl/min)	Proximal tubular reabsorption rate (nl/min)	Effective glomerular filtration coefficient ($nl\ min^{-1}mmHg^{-1}$)	Glomerular capillary pressure (mmHg)	Proximal tubular pressure (mmHg)
Diabetic rats:										
	14.0	1.09	1.15 (6%)	–	–	39.5 (40%)	19.3 (42%)	–	52.5 (5%)	10.5 (3%)
	18.8	1.11	1.64 (29%)	0.34	4.81	46.3 (52%)	25.2 (77%)	1.92	58.5 (7%)	9.2 (14%)
	18.8	1.28	1.10 (21%)	0.24	4.56	38.2 (11%)	21.2 (6%)	1.24	56.7 (10%)	9.6 (5%)
	16.3	1.44	1.16 (11%)	0.24	4.87	32.9 (15%)	16.8 (15%)	1.29	56.9 (6%)	10.9 (2%)
	8.1	1.05	1.09 (7%)	0.39	2.80	34.0 (26%)	16.0 (30%)	2.09	55.2 (6%)	10.3 (9%)
	8.7	1.04	1.17 (0%)	0.29	4.03	35.2 (24%)	16.0 (18%)	1.79	56.5 (1%)	11.1 (10%)
	10.6	1.01	1.15 (5%)	0.30	3.83	30.4 (2%)	14.0 (20%)	1.30	56.8 (2%)	10.4 (18%)
	16.6	1.15	1.19 (13%)	0.30	3.95	39.9 (4%)	23.7 (14%)	1.79	54.8 (2%)	11.0 (8%)
Mean	14.0	1.15	1.21	0.30	4.12	37.0	19.0	1.63	56.0	10.4
SEM	1.5	0.05	0.06	0.02	0.27	1.8	1.4	0.13	0.6	0.2
Control rats:										
	4.8	0.82	0.93 (21%)	0.30	3.08	23.1 (7%)	13.7 (14%)	1.37	59.5 (1%)	12.5 (5%)
	5.4	1.08	1.00 (7%)	–	–	27.9 (2%)	11.0 (6%)	–	57.7 (7%)	12.4 (1%)
	5.7	1.06	0.78 (6%)	0.38	2.06	24.2 (29%)	12.3 (28%)	1.56	56.4 (7%)	14.2 (12%)
	4.8	1.16	1.15 (6%)	0.37	3.10	41.1 (17%)	17.0 (31%)	2.01	54.7 (8%)	13.1 (6%)
	4.6	0.79	0.53 (15%)	0.17	3.12	25.6 (10%)	15.2 (13%)	1.06	51.9 (7%)	12.0 (7%)
	6.0	0.74	0.69 (5%)	0.24	2.85	26.3 (5%)	13.8 (17%)	1.24	55.7 (3%)	12.2 (5%)
	5.2	0.85	0.78 (13%)	–	–	31.5 (5%)	16.5 (1%)	–	53.6 (1%)	11.5 (3%)
	5.6	1.14	0.86 (6%)	0.23	3.74	23.8 (5%)	13.2 (4%)	1.01	58.0 (4%)	12.1 (4%)
Mean	4.8	0.96	0.84	0.28	2.99	27.9	14.1	1.38	56.0	12.5
SEM	0.3	0.06	0.07	0.03	0.22	2.1	0.7	0.15	0.9	0.3
p	<0.001	<0.05	<0.01	NS	<0.01	<0.02	<0.02	NS	NS	<0.01

Coefficients of variation given in parentheses. NS = not significant

the end of the efferent arterioles were 10.6 ± 0.3 mmHg in diabetics and 12.5 ± 0.6 mmHg in controls ($p < 0.01$).

At the end of the experiments the mean glomerular capillary pressure measured directly in the corticotomy was 52.1 ± 2.0 mmHg in diabetics ($n = 7$). The mean of the paired differences between directly measured capillary pressures and the corresponding capillary pressures measured simultaneously by the stop-flow method was 0.1 ± 1.1 mmHg which is not significant ($p > 0.09$). Likewise in three normal rats no significant difference was observed: the mean of the paired differences was 2.6 ± 1.3 mmHg.

The proximal intratubular pressure during free flow conditions was significantly reduced in the diabetic rats: 10.4 ± 0.2 mmHg in comparison with 12.5 ± 0.3 mmHg recorded in the controls ($p < 0.01$; Table 1). In contrast, the distal intratubular pressures were almost the same in the two groups: 6.6 ±0.5 mmHg ($n = 6$) in diabetics and 6.9 ± 0.5 mmHg ($n = 6$) in contols. Consequently, the pressure gradient across the loop of Henle was 3.9 ± 0.3 mmHg ($n = 6$) in diabetics which is significantly less than the value of 5.4 ± 0.5 mmHg ($n = 6$) in the controls ($p < 0.05$).

Glomerular Function

The GFR was increased in diabetics compared with controls.The mean value of GFR recorded in the left kidney subjected to micropuncture was 1.21 ± 0.06 ml/min in diabetics and 0.84 ± 0.07 ml/min in controls ($p < 0.01$). The untouched right kidney showed similar values: the mean of the difference of the paired values of GFR in the right and left kidney was 0.01 ± 0.04 ml/min in diabetics and 0.06 ± 0.04 ml/min in controls.

The filtration fraction of the left kidney was almost the same in diabetics ($n = 7$) and controls ($n = 6$) being 0.30 ± 0.02 and 0.28 ± 0.02 respectively ($p > 0.5$). Accordingly, renal plasma flow was substantially higher in diabetics than in controls: 4.1 ± 0.3 versus 3.0 ± 0.2 ml/min ($p < 0.01$; Table 1).

The values of GFR in single nephrons showed a similar proportional increase between diabetics and controls being 37.0 ± 1.8 and 27.9 ± 2.1 nl/min respectively ($p < 0.02$). Filtration pressure equilibrium [6] was not reached in the glomerular capillaries of either group of rats: the hydraulic pressure in the glomerular capillaries less the colloid osmotic pressure at the end of the glomerular capillaries exceeded the proximal intratubular pressure by approximately 15 mmHg in each group. Consequently, a unique value of the effective glomerular capillary filtration coefficient could be calculated for each group: These values showed no significant difference between diabetic (0.027 ± 0.002 nl s^{-1} $mmHg^{-1}$, $n = 7$) and control rats (0.023 ± 0.003 nl s^{-1} $mmHg^{-1}$, $n = 6$; $p = 0.22$).

Proximal Tubular Function

The rate of fluid reabsorption in the proximal convoluted tubule in diabetic animals was 19.0 ± 1.4 nl/min which is significantly higher than the value in controls of 14.1 ± 0.7 nl/min ($p < 0.02$; Table 1). Hence, glomerulo-tubular balance was maintained in the diabetic rats with a fractional reabsorption of 0.51 ± 0.02 compared with 0.52 ± 0.02 obtained in controls. The flow rate at the end of the proximal convoluted tubule in diabetic rats was 17.9 ± 0.7 nl/min which is significantly higher than the value of 13.8 ± 1.7 nl/min recorded in controls ($p < 0.05$).

Systemic Parameters

The preoperative levels of blood glucose were 14.0 ± 1.5 mmol/l in diabetic rats and 4.8 ± 0.3 mmol/l in controls ($p < 0.001$; Table 1). The arterial haematocrit and protein concentrations were identical in the two groups: 0.48 ± 0.01 and 51.5 ± 1.9 g/l respectively in diabetic and 0.48 ± 0.01 and 53.3 ± 1.8 g/l respectively in control animals.

The mean body weight of 232 ± 9 g in diabetic rats was not significantly different from the control value of 238 ± 10 g. In contrast, the weight of the left kidney was 1.15 ± 0.05 g in diabetic and 0.96 ± 0.06 g in control animals ($p < 0.05$; Table 1).

Discussion

The experimental results confirm that GFR, renal plasma flow and kidney weight are increased in the insulin- treated streptozotocin diabetic rat in poor metabolic control but without ketonuria [16]. These results agree closely with observations made in human insulin-dependent diabetes mellitus [7, 21, 22]. This suggests that the streptozotocin diabetic rat may be considered a useful experimental model for studying renal function in human insulin-dependent diabetes mellitus.

GFR is determined by the product of the effective glomerular filtration coefficient and the mean ultrafiltration pressure across the membrane. The effective glomerular filtration coefficient is determined by the product of the hydraulic conductance and the glomerular surface area available for ultrafiltration. The mean ultrafiltration pressure is determined by the hydraulic pressure difference across the glomerular

membrane, the renal plasma flow and the arterial plasma protein concentration [10]. Consequently, GFR depends on the effective glomerular filtration coefficient, the renal plasma flow, the plasma colloid osmotic pressure and the hydraulic pressures in the glomerular capillaries and in the earliest part of the proximal tubule. The increases in renal plasma flow and the transglomerular hydraulic pressure in the diabetic rats both cause an increase in the mean ultrafiltration pressure across the glomerular membrane. Using a mathematical model of glomerular ultrafiltration [10], it can be calculated that the observed rise in ultrafiltration pressure can account for only about half of the rise in GFR. The increase in effective glomerular filtration coefficient (+19%) which was observed probably failed to reach statistical significance because of the limited number of observations.

The findings of increased kidney weight, GFR, renal plasma flow and transglomerular hydraulic pressure agree with the results of Hostetter et al. [16]. The rise in transglomerular hydraulic pressure difference in the present experiments was caused by a reduction in the proximal intratubular pressure while the increase observed in the former study [16] resulted from an increase in glomerular capillary pressure. It is unlikely that the different glomerular capillary pressures recorded in the present and in the earlier study [16] are related to our use of the stop-flow method since almost identical pressures have been recorded by this method and by direct pressure measurement [3, 5, 24]. The values for the effective glomerular ultrafiltration coefficient obtained in the present experiments are substantially lower than those recorded in the previous study [16]. This discrepancy may be related to the higher glomerular capillary pressures found here which, in turn, may be related to a difference in salt intake [11, 27] or to differences in genetic constitution between the rats used in various laboratories [2, 32].

The increase in renal plasma flow in our diabetic rats was caused by proportional decreases in the preglomerular and postglomerular hydraulic resistances, since the glomerular capillary pressure was the same as in the control rats.

The decrease in proximal intratubular pressure associated with an increased flow rate of tubular fluid to the loop of Henle indicates that the hydraulic resistance of the tubules is reduced in diabetes.

The hypertrophy of the diabetic kidney may be the cause of the changes in the variables determining GFR. A similar relationship between GFR and kidney mass is also observed in experimental renal hypertrophy after unilateral nephrectomy [9, 15]. In mature, growing rats the increase in kidney weight is associated with a rise in effective glomerular filtration coefficient and decreases in the hydraulic resistances of both the afferent and efferent arterioles [31], leading to increased renal plasma flow. The increase in effective glomerular filtration coefficient is related to an increase in the surface area of the glomerular membrane [23]. This correlates with observations in glomeruli of diabetic rats [28] and human insulin-dependent diabetes mellitus [18]. The decreased hydraulic resistance of the tubules may be related to the increase in tubular dimensions [28, 29]. The cause of the kidney hypertrophy in diabetes remains unknown. It may be related to the increased serum concentration of growth hormone observed in insulin-dependent mellitus [14] or may be a secondary adaption to increased function [15].

Renal plasma flow and GFR have been found to be reduced in untreated streptozotocin diabetic rats with ketonuria and severe hyperglycemia [16, 19]. Similar observations have been made in insulin-dependent diabetic patients in ketoacidosis [26]. These findings, however, are probably a result of the severe dehydration seen in this condition, and thus do not conflict with the findings reported here.

Acknowledgements. Mrs. Lone Durkop and Mr. Ole Kristensen provided technical assistance with the treatment and maintenance of the animals. Mrs. Dorte Davidsen and Mrs. Jytte Amtorp provided laboratory assistance. The study was supported by a grant from Weiman's Legacy.

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Received: 30 October 1980
and in revised form: 4 June 1981

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