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Effects of Dietary Salt on Blood Pressure, Heart Rate, Extracellular Fluid Volume and Glomerular Filtration Rate in Diabetic Rats

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Abstract: In the present study, we aimed to investigate the effects of dietary salt restriction and loading on extracellular fluid volume (ECFV), blood pressure (BP), heart rate (HR), glomerular filtration rate (GFR) and renal hypertrophy in diabetic rats. Diabetes was induced by injection of streptozotocin (STZ, 65 mg/kg, iv) into male Wistar rats. Four groups were formed: a) the diabetic rats given a standard rat diet (DC), b) the diabetic rats given a high-salt diet (DHS), c) the diabetic rats given a low-salt diet (DLS), d) the nondiabetic rats given a standard rat diet (C). Salt loading and salt restriction were started 7 days after STZ injection and continued for a one-week. Diabetes did not affect ECFV and GFR values significantly, but it led to renal hypertrophy, a reduction in blood pressure ($p<0.05$) and a reduction tendency in HR. Salt loading caused a decrease in diastolic blood pressure (DBP) while salt restriction caused an increase in DBP, but the differences were statistically non-significant. However, these changes in opposite directions caused a significant difference between DLS and DHS. Both salt loading and restriction increased ECFV ($p<0.05$). GFR increased in DLS and tended to increase in DHS. We determined a significant correlation between ECFV and HR only in C ($r=0.72$, $p<0.05$) and DHS ($r=-0.95$, $p<0.001$) . We concluded that dietary salt quantity can affect DBP and ECFV levels and the alterations in ECFV may lead to changes in GFR at diabetes. In addition, both diabetes and dietary salt may modify the feedback mechanisms that operate between ECFV and HR.

Key Words: Diabetes, blood pressure, extracellular fluid volume, glomerular filtration rate, dietary salt.

Introduction

Volume receptor reflex often is impaired in diabetes. In previous studies, it has been concluded that STZ-treated rats have impaired diuretic, natriuretic (1-3) and plasma atrial natriuretic peptide (ANP) release (4) responses to volume expansion. In addition, diabetes often leads to renal hypertrophy and hyperfiltration but their causes are not exactly clear (5-8). The adaptive changes that may be due to increased fluid and electrolyte turnover have been considered as possible reasons of renal hypertrophy (6, 9-11). Thus, it seems that Na^+ is a key element in the process of renal hypertrophy, perhaps causing the increases in glomerular filtration rate (GFR) (9).

Generally, STZ-induced diabetic rats have volume expansion (12). In diabetics, it has been accepted that the attenuated natriuretic response to ANP and the enhanced sodium retention during volume contraction could lead to expanded extracellular fluid volume (ECFV) (13).

In previous studies, low blood pressure (BP) and bradycardia have often been recorded in diabetes, when the measurements were made directly intra-arterially (9, 14). On the other hand, a high or normal BP level and normal heart rate (HR) have been also reported in some experiments (15-17). Differences among BP measurements may be due to different salt intakes. However, salt content of the diet is very rarely reported in studies on diabetes. In addition, the abnormal fluid and electrolyte handling that have effects on blood volume may lead to the disturbances that are associated with cardiovascular control in diabetes (9, 18).

We were unable to find any literature about the effects of different salt diets on GFR, body fluid volumes and cardiovascular parameters, together, in diabetic rats. In the present study, because of high Na^+ turnover we evaluated the effects of low and high-salt diets on GFR, renal hypertrophy, ECFV, BP and HR values in diabetes.

Table 1. Body weights, plasma glucose level, extracellular fluid volume, glomerular filtration rate and kidney weight in experimental groups.

GROUP	BW_1 (g)	BW_2 (g)	Glucose (mmol/L)	ECFV (mL/kg)	GFR (mL/min) (100 g BW)	RW (mg)
C	307.11 ±11.26	320.11 ±32.68	10.88 ±1.67	331.20 ±24.01	0.51 ±0.19	695.78 ±65.49
(n=9)					(n=6)	
DC	314.86 ±19.88	252.57 ±19.58$^{\phi}$*	39.71 ±6.61$^{\#}$	353.15 43.65	0.42 ±0.14	898.00 ±78.97$^{\#}$
(n=6)						
DHS	305.13 ±6.33	238.13 ±17.74$^{\phi}$*	38.51 ±6.44$^{\#}$	415.04 ±45.64$^{\#}$**	0.85 ±0.55	913.50 ±91.02$^{\#}$
(n=8)					(n=6)	
DLS	300.00 ±8.70	233.00 ±12.33$^{\phi}$*	37.66 ±7.32$^{\#}$	415.86 ±27.91$^{\#}$**	0.98 ±0.46$^{\#}$**	932.00 ±49.87$^{\#}$
(n=8)					(n=6)	

BW_1: the body weight one day before injection of STZ or vehicle, BW_2: the body weight 14 days after injection of STZ or vehicle. ECFV: extracellular fluid volume, GFR: glomerular filtration rate, RW: renal weight; C: Nondiabetic control; DC: Diabetes+standard diet; DHS: Diabetes+high-salt diet; DLS: Diabetes+low-salt diet. Values are means±SD. * $p < 0.05$ v pre-injection values, **$p< 0.05$ v DC, $^{\#}p < 0.05$ v C, $^{\phi}p<0.01$ v C.

Materials and Methods

Male Wistar rats (obtained from the Medical and Experimental Research Center, Adana), weighing 307±12.75 g (mean±SD), were used. The rats were housed at constant room temperature (24°C) and on a 12:12 h light-dark cycle. The animals received standard rat pellets (22% protein, 0.50% NaCl) and tap water until they were given different diets. Initially, systolic blood pressures (SBP) were measured by an indirect tail-cuff method (Rat Tail BP Monitor, Harvard, Edenbridge, Kent). For this purpose, the rats were warmed for 5 minutes at 34°C. Then, they were placed in a plastic restrainer for SBP and HR measurements. Normotensive rats (the rats with SBP values less than 130 mmHg) were used. Streptozotocin (STZ) (Sigma Chemical, St. Louis, MO) was dissolved in citrate buffer (0.1 M, pH 4.5) at a concentration of 65 mg/mL, immediately prior to injection. Either STZ (65 mg/kg; diabetic groups, n=24) or citrate buffer vehicle (nondiabetic control group, C, n=9) were injected into the animals via the left jugular vein under light ether anesthesia. Nondiabetic control rats received standard rat pellets and tap water during the study. One week after STZ injection, diabetic rats were randomly assigned to one of three groups: 1) those given standard rat pellets and tap water (DC, n=7), 2) those given a high-salt diet [1% NaCl as drinking water and low-salt pellets (0.02% NaCl)], (DHS, n=8), and 3) those given a low-salt diet (distilled drinking water and low-salt pellets), (DLS, n=9). Salt loading and salt restriction were started 7 days after STZ injection and continued for one-week. Two days after the injection of either STZ or vehicle, urine samples were tested with multistix (Diagnostix, Bayer, Germany) to detect glucosuria, an indicator of diabetes.

Blood pressure, GFR and ECFV measurements were performed under pentobarbital sodium (75 mg/kg, i.p.) anesthesia 14 days after injections of STZ. Body temperature was maintained by a heating lamp. After

Table 2. Blood pressures and heart rates in experimental groups.

GROUP	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (beats/min)
C	132.44	85.00	100.82	349.78
(n=9)	±6.42	±6.12	±5.52	±37.74
DC	102.50	68.33	78.39	295.67
(n=6)	±26.03*	±13.29*	±18.64*	±66.96
DHS	103.13	58.13	73.12	302.63
(n=8)	±17.92*	±7.04*#	±9.69*	±45.63
DLS	107.50	73.13	84.58	299.50
(n=8)	±15.81*	±11.00*	±11.54*	±39.85

SBP: Systolic, DBP: Diastolic, MAP: Mean, blood pressures. HR: Heart rate. C: Nondiabetic control; DC: Diabetes+standard diet; DHS: Diabetes+high-salt diet; DLS: Diabetes+low-salt diet. Values are means±SD. *$p < 0.05$ v C, #$p < 0.05$ v DLS.

tracheostomy, the animals were allowed to breathe independently. The left femoral artery was cannulated with PE-50 tubing (Clay-Adams, Parsipanny, NJ) which was connected to a pressure transducer and a recorder (Bioscience, Washington) for continuous recording of arterial blood pressure and heart rate. Mean arterial blood pressure (MAP) was accepted as the sum of 1/3 pulse pressure with diastolic pressure. Tubings (PE-50) were inserted into the left femoral and jugular veins for the infusions of drugs and isotonic NaCl, respectively. The fluids in the cannulas were heparinized (50 IU/mL). The urinary bladder was catheterized (PE-90) for urine collection. After the jugular vein connection, 0.9% NaCl was continuously infused (Infusion Pump, Model 210, Cole-Parmer, USA) into the animal throughout the experiment at a rate of 0.02 mL/min for the compensation of insensible fluid losses.

Sodium thiocyanate (NaSCN) and inulin were used for the determination of ECFV (19) and GFR (20), respectively, by spectrophotometry. For these purposes a control blood specimen (0.3 mL) was withdrawn at the end of the stabilization period (30 minutes). After 5% inulin (1.2 mL/kg) and 0.5 mL 1% NaSCN solutions in isotonic saline were infused as i.v. bolus into the animals, 3.33% inulin solution in 0.9% NaCl was continuously infused (0.01 mL/min) for one hour. Three blood samples (0.2 mL) were withdrawn 0, 16 and 48 minutes after the end of the last period for determination of plasma NaSCN (only in the first sample) and inulin concentrations (in each of the samples). Whenever blood was withdrawn, it was centrifuged at 4°C and the volume deficit was compensated with erytrocytes that were suspended in 0.9% NaCl. Urine was collected during two successive 32 minute periods to determine the amount of excreted inulin. At the end of urine collection, 3 mL arterial blood was withdrawn for the determination of glucose. The kidneys were removed and weighed after separation from their capsules. The plasma obtained was stored at -80°C until assayed. Inulin clearance for each period was calculated and the mean of the two periods was accepted as GFR. Plasma glucose level was determined with by the glucose oxidase method (Sclavo, Siena, Italy).

Statistics: Results are expressed as means ± SD. The differences between groups were evaluated with Kruskal-Wallis ANOVA and the Mann Whitney U test. The Wilcoxon matched pairs test was used to evaluate the changes at different times in the same group. Linear regression analysis was applied between parameters. Differences were considered statistically significant at $p<0.05$.

Results

STZ injected rats exhibited the characteristic symptoms of diabetes. Body weights that were measured

before and after STZ or vehicle injections, plasma glucose, ECFV, GFR and renal weight values are shown in Table 1. The nondiabetic group gained weight, whereas the diabetic groups lost weight. Body weight was greater in the control group than in each diabetic group ($p<0.01$) and not significantly different between the diabetic groups. All STZ-treated rats had glucosuria (> 110 mg/mL urine). Plasma glucose level was greater in each diabetic group than the nondiabetic control group ($p<0.001$) and not significantly different between the diabetic groups. No significant differences were found between C and DC with regard to ECFV and GFR. In DHS and DLS, ECFV was greater than C and DC ($p<0.05$). GFR was greater in the DLS group than in the C and DC groups ($p<0.05$). Kidney weight increased in the diabetic groups compared with C ($p<0.05$) but neither low- nor high-salt diets significantly affected kidney weight in the diabetic groups when they were compared with DC.

SBP, DBP and MAP were smaller in each diabetic group than C ($p<0.05$) but no significant difference was present between DC and the other the diabetic groups (Table 2). When diabetic groups were put in order of salt content in their diets, DBP and MAP tended to decrease as the salt content in the diet increased (e.g. with regard to DBP or MAP level, the order was DLS>DC>DHS). There was a significant difference between DLS and DHS with regard to DBP ($p<0.05$). HR tended to decrease in each diabetic group compared with the nondiabetic control group but the differences were nonsignificant. HR showed no significant difference between the diabetic groups.

Only in DC, there was an inverse correlation between glucose and both DBP and MAP ($r=-0.85$, $p<0.05$). There was a positive correlation between ECFV and HR values in C ($r=0.72$, $p<0.05$), but a strong negative correlation in DHS ($r=-0.95$, $p<0.01$).

Discussion

Over a period of 2 weeks, the weight of diabetic rats decreased while the weight of the nondiabetic control group tended to increase. This was an expected result because of metabolic changes in diabetes. There was no significant differences between the glucose levels of diabetic groups. For this reason, we can accept that the effects of low- and high-salt diets on ECFV, GFR and BP levels in diabetics are not dependent on plasma glucose levels.

Diabetes did not lead to a significant increase in ECFV, but it has been reported that diabetes increases ECFV in another study (21). The cause of the difference may be due to the short duration of diabetes in the present study. However, it is an interesting condition in which both high-and low-salt diets caused the increases in ECFV of diabetic rats. In other words, although diabetes did not affect ECFV significantly, it caused the rats to be unable to maintain their ECFV in the normal range under both low and high dietary-salt conditions. Consequently, we can expect that body fluid volume control mechanisms fail to balance the ECFV level in diabetic rats under stress conditions.

Generally, severe diabetes decreases GFR (22), but nonsevere diabetes increases it (5, 6). Thus, GFR may be normal, low or high, depending on the severity of diabetes. In our study, the unchanged GFR in the diabetic control group can be understood if we consider this wide variation in GFR values of diabetics. Although we did not determine a significant increase in GFR and ECFV in the diabetic control group, an increase or a tendency to increase in GFR together with an increase in ECFV was recorded at both salt restriction and loading stages. This result confirms the conclusion that ECFV is an important parameter that affects GFR in diabetes (23). An increase in GFR parallel to that in ECFV is an acceptable association because volume expansion is an important stimulator of ANP secretion (24) and ANP plays an important role in the development of hyperfiltration in diabetes (25). However, in diabetics with salt loading, ECFV significantly increased, but GFR did not. Therefore, it can be accepted that all changes in GFR are not only due to volume expansion. In other words, we can conclude that salt restriction increases GFR also by mechanisms other than the increase in ECFV since salt restriction caused a significant increase in GFR. This result is consistent with those of authors who state that the change in GFR could not be explained only by sodium and volume status (26) and that a low-salt diet increases GFR (27) in diabetes.

Diabetes caused growth of the kidneys. This result follows that of previous studies in which renal hypertrophy was determined (5, 7). The increased renal weight is partly due to a decrease in body weight (BW) gain because it changes the renal weight/BW ratio. Since low- and high- salt diets did not affect the amount of this hypertrophy, we can accept that the amount of salt intake is not important in the formation of renal hypertrophy for short-term diabetes. However, the determination of the total protein concentration in kidneys can give us better information about renal hypertrophy because salt can cause changes in fluid-electrolyte turnover that may lead to microscopic changes in renal tissue. It has been

reported that both high-salt (27) and low-salt (28) diets caused renal growth in diabetes. But in the first study, the severity of diabetes was less and the duration of diabetes longer than in our present study, and in the second, there was insulin-treated diabetes.

We recorded a reduction in the blood pressure of the diabetics. This result agrees with the conclusions of studies which had used the direct technique for measurement of blood pressure (29-31). Normotension or hypotension with lower total peripheral resistance (TPR) have been reported in diabetes, although it has been generally determined that hyperglycemia did not affect or increase cardiac output (29, 32). Hence, it seems that diabetes causes hypotension principally by decreasing TPR. Actually, the changes that decrease TPR are more prominent in diabetes (10, 26, 31), although some findings show an increase of vascular constrictor response (e.g. in vitro increases at vasoconstrictor response to norepinephrine) (33). Also, a decrease in the response of renin-angiotensin-aldosterone system activity to saline infusion in diabetes has been reported (34). There was a strong inverse correlation between DBP and glucose levels in the diabetic control group in our study and TPR is the principal determining factor of DBP (35). Hence, it could be considered that hyperglycemia may change mean blood pressure by affecting DBP. Significantly, neither high- nor low-salt diets affected SBP and MAP in diabetics. In another two studies also, it has been concluded that a high sodium diet did not affect blood pressure in diabetic rats (17, 27). However, in our study, when diabetic groups were arranged according to the salt contents of their diets, it was determined that DBP and MAP tended to decrease from the low-salt group to the high-salt group. The difference between these two diabetic groups was statistically significant with regard to DBP. Consequently, in diabetics, it can be accepted that salt loading tends to reduce DBP, but salt restriction tends to increase it. In addition, this result partly confirms the suggestion that different salt amounts in diets may lead to different BP measurements in studies on diabetes (9). Although ECFV was increased by both low- and high-salt diets in diabetics, DBP tended to increase in a low-salt diet but to decrease in a high-salt diet. Therefore, it is likely that different salt diets affect blood pressure via mechanisms other than those just affecting ECFV. In both low- and high salt diet conditions, the increase in ECFV may lead to an increase in ANP and a decrease in plasma renin activity (24). Thus, the sympathetic nervous system activity which is a determinative factor of TPR, was possibly affected by both low-salt and high-salt diets because of reasons other than just increases in ECFV. Actually, there is an attenuated suppression in reflex response to stimulation of sympathetic nervous system after dietary salt restriction in diabetic patients (36).

HR tended to decrease in the diabetic control group but the difference was not significant. Many authors have reported that diabetes decreased HR (30-32, 37), while some researchers did not find diabetic bradycardia (15). Consequently, we can state that the pathophysiologic conditions in diabetes may decrease HR but the amount of the decrease may vary possibly due to different durations and severity of diabetes. The duration and severity may affect the desensitization (38) and the reduction (39, 40) of β-adrenergic receptors, plus baroreflex mechanisms that control the heart rate (15), in diabetes. In addition, the alterations in plasma level of AVP partly depend on volume status that may change during the course of diabetes (9) and AVP may affect HR (16). We can state that the salt quantity of diet does not play an important role in alterations of HR in short-term diabetes because both low- and high-salt diets did not cause a significant effect on HR. However, there was a strong inverse correlation between ECFV and HR in the high-salt diabetic group and a positive correlation in the nondiabetic control group. On the other hand, there was no correlation between the two parameters in both the diabetic control and low-salt diabetic groups. Thus, the function of feedback mechanisms that operate between ECFV and HR could be modified by both diabetes and dietary salt.

In summary, changes in the level of salt in the diet may cause alterations in ECFV and GFR in diabetes. However, the effects of salt restriction and loading on these parameters may be in the same direction. In addition, it is concluded that the DBP levels in diabetes could be decreased with a high-salt diet and, both diabetes and dietary salt can modify feedback mechanisms that operate between ECFV and HR. More detailed experiments that include the effects of dietary salt on hormonal balances may contribute greatly in clarifying the effects of salt on ECFV and DBP in diabetes.

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