Effect of Gonadectomy on the Development of Diabetes Mellitus, Hypertension, and Albuminuria in the Rat Model

M. Iwase, M. Wakisaka, M. Yoshinari, Y. Sato, H. Yoshizumi, K. Nunoi, and M. Fujishima

Spontaneously hypertensive rats (SHR) given streptozotocin (STZ) neonatally developed genetic hypertension and overt hyperglycemia after the onset of puberty. In the present study, gonadectomy was performed before puberty in both males and females of this animal model. Orchidectomy suppressed the development of hypertension in vehicle-treated and STZ-treated SHR (systolic blood pressure at 11 weeks of age: 209 ± 5 mm Hg in the intact vehicle group *v* 187 ± 6 mm Hg in the orchidectomized vehicle group, $P < .01$; 211 ± 14 mm Hg in the intact STZ group *v* 182 ± 4 mm Hg in the orchidectomized STZ group, $P < .001$). Furthermore, orchidectomy ameliorated the development of overt hyperglycemia in STZ-treated SHR (nonfasting plasma glucose at 12 weeks of age: 22.1 ± 0.7 mmol/L in the intact group *v* 16.1 ± 2.4 mmol/L in the orchidectomized group, $P < .05$). On the other hand, orchidectomy did not affect glucose tolerance in vehicle-treated SHR, but attenuated the insulin response to an oral glucose load ($P < .05$). Orchidectomy significantly decreased urinary albumin excretion and kidney weight in both the vehicle and the STZ groups. Ovariectomy significantly increased body weight gain irrespective of STZ treatment. However, ovariectomy had no effect on hypertension, hyperglycemia, albuminuria, or kidney weight in either vehicle or STZ groups. This study demonstrated that gonadectomy had protective effects against development of hypertension, hyperglycemia, and albuminuria in males but not in females. This suggests that sex hormones may be important as a link between diabetes mellitus and hypertension in males.

NON-INSULIN-DEPENDENT diabetes mellitus (NIDDM) and essential hypertension frequently coexist.[1] However, the mechanisms for a link between the two diseases have not been fully understood. Hypertension is more prevalent in diabetic men than in diabetic women less than 50 years of age, and more common in women thereafter.[2] Furthermore, it is well known that sex hormones modulate insulin sensitivity in humans. Men and women receiving anabolic steroids[3,4] and women taking oral contraceptives[5] often develop insulin resistance. Regarding endogenous sex hormones, hyperandrogenicity in women is associated with insulin resistance,[6] and a low sex hormone–binding globulin concentration, an indicator of relative hyperandrogenicity, is a powerful independent risk factor for development of NIDDM in women.[7,8] Many studies have shown that insulin resistance is one of the most important pathogenetic factors for NIDDM and hypertension.[9,10] However, the role of sex steroid in the coexistence of NIDDM and hypertension still remains to be elucidated.

Spontaneously hypertensive rats (SHR) were reported to have insulin resistance similar to that observed in patients with essential hypertension.[11] We previously reported an animal model of genetic hypertension associated with diabetes mellitus by administering streptozotocin (STZ) to neonatal SHR.[12] In this model, overt hyperglycemia and hypertension gradually developed after the onset of puberty in both males and females. In the present study, gonadectomy was performed before puberty in both male and female neonatally STZ-treated SHR. Furthermore, since sex hormones may modify the hemodynamics and growth of rat kidney,[13] we also evaluated the effects of gonadectomy on urinary albumin excretion in diabetic SHR, which developed renal injury in a more accelerated form than nondiabetic SHR.[14] We found that gonadectomy had protective effects on the development of hypertension, hyperglycemia, and albuminuria in males but not in females.

MATERIALS AND METHODS

Animals

SHR were from our inbred colony, which has been maintained in our laboratory since 1973. The rats were bred in specific pathogen-free conditions (lights on 8 AM to 8 PM). They had free access to tap water and a standard chow diet (Clea Japan, Tokyo, Japan) that contained carbohydrate (51.6%), protein (24.8%), minerals (7.0%), fat (4.4%), and cellulose (3.5%). Animals were cared for as directed by the guidelines of Kyushu University. Two-day-old SHR were injected intraperitoneally with 75 mg/kg body weight STZ (Upjohn, Kalamazoo, MI) dissolved in 0.1 mol/L citrate buffer, pH 4.5.[12] Control SHR received the vehicle alone. The neonates were left with their own mothers. Male and female SHR of either the vehicle-treated group (n = 5) or the STZ-treated group (n = 7) were killed at 4 and 10 days of age. The pancreas was immediately removed and stored at −20°C until pancreatic immunoreactive insulin (IRI) content was determined. At 3 weeks of age, the rats were divided into four groups, namely intact vehicle-treated SHR (five males, five females), gonadectomized vehicle-treated SHR (five males, five females), intact STZ-treated SHR (six males, 11 females), and gonadectomized STZ-treated SHR (eight males, seven females). Either orchidectomy or ovariectomy was performed under ether anesthesia, whereas the intact groups received no sham operation. The surgery was well tolerated, and body weight did not differ between intact and gonadectomized SHR at weaning (4 weeks of age). Rats were killed by exsanguination through the inferior vena cava under pentobarbital anesthesia in a

From the Second Department of Internal Medicine, Faculty of Medicine, Kyushu University, Fukuoka, Japan.

Submitted October 22, 1994; accepted June 14, 1995.

Presented at the 15th International Diabetes Federation Congress, Kobe, Japan, November 6-11, 1994.

Address reprint requests to M. Iwase, MD, Department of Medical Cell Biology, Uppsala University, Biomedicum, Box 571, S-751 23 Uppsala, Sweden.

0026-0495/96/4502-0004$03.00/0

fed state at 12 weeks of age, and then the pancreas and kidneys were immediately removed and weighed.

Measurements

Body weight was measured weekly. The awake systolic blood pressure was measured by the indirect tail-cuff method between 3 and 6 PM biweekly from 5 weeks of age to 11 weeks of age by the same investigator (Mk-1000; Muromachikikai, Tokyo, Japan). The rats were warmed to 37°C for 10 minutes, and then three stable consecutive measurements of blood pressure were averaged. Blood was obtained by cardiac puncture at 4 and 10 days of age, by snipping the tail vein in a fed state (6 PM) from 3 through 12 weeks, and after overnight fasting at 12 weeks. An oral glucose tolerance test (2 g/kg body weight in 20% glucose solution) was performed through an orogastric tube after overnight fasting in intact or gonadectomized vehicle-treated groups. Urine was collected and food intake was measured for 24 hours by a metabolic cage at 12 weeks of age. Glucose level was measured by the glucose oxidase method. IRI level was measured by radioimmunoassay (Insulin Riabead; Dainabot, Tokyo, Japan) with rat insulin standard (Novo Research Institute, Bagsvaerd, Denmark) in duplicate. Intraassay and interassay variations were 8.0% and 7.7%, respectively. Pancreatic IRI content was determined after acid ethanol extraction. Urinary albumin level was measured by an enzyme immunoassay with rat albumin standard, and intraassay and interassay variations were within 8%, respectively. Serum levels of free testosterone and estradiol were measured by commercial radioimmunoassay kits (Coat-A-Count; Diagnostic Products, Los Angeles, CA).

Statistical Analysis

ANOVA was used to compare multiple groups. Differences between the two groups were tested by Fisher's protected least-significant difference only when found to be significant by ANOVA. The difference in serum testosterone levels between intact and orchidectomized groups was tested by a Scheffe-type multiple-comparison test for rank values of variables using a SAS (Cary, NC) statistical package.[15] The results were considered significant when P was less than .05. Values are expressed as the mean ± SEM.

RESULTS

Pancreatic IRI content per whole gland was markedly reduced in STZ-treated groups as compared with vehicle-treated groups at 4 days of age (4 ± 0 *v* 97 ± 20 mU, $P < .001$, in males, n = 7 and n = 5, respectively; 6 ± 2 *v* 112 ± 23 mU, $P < .001$, in females, n = 7 and n = 5, respectively) and at 10 days of age (23 ± 5 *v* 156 ± 33 mU, $P < .001$, in males, n = 7 and n = 5, respectively; 22 ± 3 *v* 226 ± 25 mU, $P < .001$, in females, n = 7 and n = 5, respectively). However, there were no significant differences in the changes in pancreatic IRI content in response to the STZ insult between male and female SHR.

Figure 1 shows the effects of orchidectomy on body weight gain in vehicle-treated and STZ-treated groups. In the vehicle group, body weight gain was significantly reduced in orchidectomized SHR as compared with intact SHR from 8 to 12 weeks of age. By contrast, in the STZ group, the difference was statistically significant only at 8 weeks of age. As depicted in Fig 1, body weight was significantly increased in ovariectomized SHR as compared with intact SHR in the STZ group, as well as in the vehicle group.

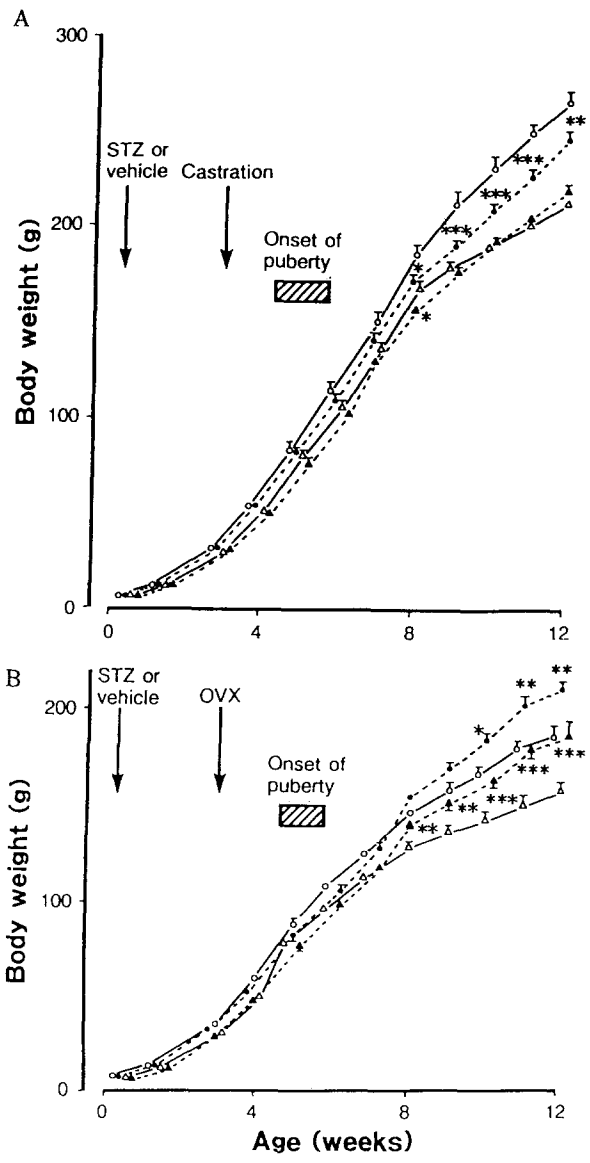

Fig 1. Changes in body weight for intact and gonadectomized SHR treated neonatally with STZ (△ and ▲, respectively) or vehicle alone (○ and ●, respectively). (A) Males; (B) females. *$P < .05$, **$P < .01$, ***$P < .001$: *v* intact rats in the corresponding group.

Figure 2 shows the effect of orchidectomy on systolic blood pressure in vehicle-treated and STZ-treated SHR. Systolic blood pressure was significantly reduced by orchidectomy both in vehicle-treated and in STZ-treated groups from 9 to 11 weeks. In contrast, ovariectomy had no effect on systolic blood pressure in vehicle-treated and STZ-treated groups (Fig 2).

Nonfasting plasma glucose levels in the STZ-treated group did not differ between intact and orchidectomized SHR up to 8 weeks (Fig 3). However, thereafter, plasma glucose significantly increased in the intact group as compared with the orchidectomized group. In the vehicle group, no significant differences were seen in plasma glucose levels between intact and orchidectomized SHR.

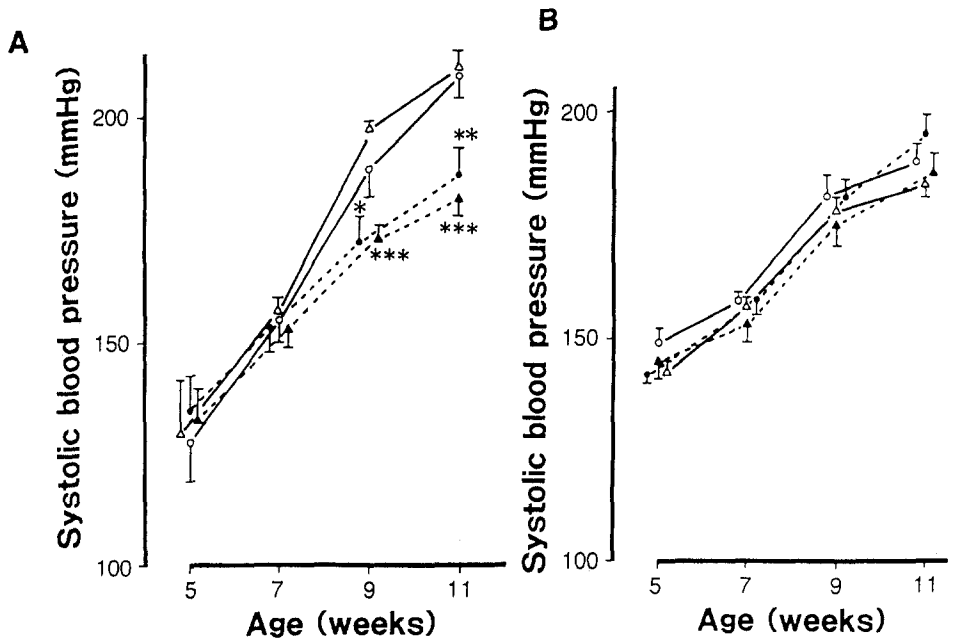

Fig 2. Changes in systolic blood pressure for intact and gonadectomized SHR treated neonatally with STZ (△ and ▲, respectively) or vehicle alone (○ and ●, respectively). (A) Males; (B) females. *$P < .05$, **$P < .01$, ***$P < .001$: v intact rats in the corresponding group.

Ovariectomy had no effect on nonfasting plasma glucose in vehicle-treated and STZ-treated groups (Fig 3).

Figure 4 shows oral glucose tolerance test results in intact or orchidectomized vehicle-treated groups at 12 weeks of age. Plasma glucose levels were not significantly different between intact and orchidectomized groups. However, serum IRI was significantly lower in the orchidectomized group than in the intact group at 60 minutes after glucose load. The ratio of total serum IRI to total plasma glucose was significantly lower in the orchidectomized group than in the intact group (0.45 ± 0.08 v 0.25 ± 0.03, $P < .05$). On the other hand, ovariectomy did not affect plasma glucose or serum IRI levels during an oral glucose tolerance test in the vehicle-treated group (Fig 4).

Table 1 shows some characteristics of the 12-week-old intact or orchidectomized SHR treated with vehicle or STZ at 2 days of age. Serum levels of free testosterone showed large variations in intact groups, but were significantly reduced by orchidectomy in both vehicle and STZ groups. Serum estradiol was significantly increased by orchidectomy in vehicle-treated SHR. Food intake tended to be reduced in orchidectomized groups as compared with intact groups, although the differences were not statistically significant. Urinary glucose excretion was significantly reduced in the orchidectomized STZ group as compared with the intact one. Overnight-fasted plasma glucose and serum IRI levels did not significantly differ among groups. Pancreatic IRI content per unit wet weight was markedly reduced in STZ-treated groups. Orchidectomy did not affect pancreatic IRI content in either vehicle or STZ groups. In addition, serum total cholesterol levels did not differ among the groups.

Ovariectomy significantly decreased serum free testosterone and estradiol levels in both vehicle and STZ groups (Table 2). Serum estradiol was significantly reduced in STZ-treated SHR as compared with vehicle-treated SHR in the intact group, although the stage of estrus was not determined in the present study. Food intake did not differ among the four groups. Ovariectomy did not significantly change the amount of urinary glucose excretion, overnight-fasted plasma glucose and serum IRI levels, or pancreatic IRI content per unit wet weight in either vehicle-treated or STZ-treated groups. Total cholesterol was significantly increased by ovariectomy and was significantly higher in STZ-treated groups than in vehicle-treated groups.

Kidney weight and urinary albumin excretion are shown in Table 3. Orchidectomy significantly reduced kidney weight in both vehicle and STZ groups. Furthermore, orchidectomy significantly decreased urinary albumin excretion as well. Kidney weight and urinary albumin excretion were significantly increased in STZ groups as compared with vehicle groups. Kidney weight and urinary albumin excretion were not changed by ovariectomy, although they were significantly greater in STZ-treated groups than in vehicle-treated groups (Table 4).

DISCUSSION

SHR given STZ during the neonatal period developed genetic hypertension and overt hyperglycemia after the onset of puberty and had increased kidney weight and urinary albumin excretion in adulthood in both males and females. The present study demonstrated that gonadectomy had protective effects against the development of hypertension, hyperglycemia, nephromegaly, and albuminuria in males but not in females.

Sexual dimorphism of blood pressure in SHR was reported to be androgen-dependent[16,17] The exact mechanism by which androgens act to increase blood pressure is still unknown, but some studies suggest that sex hormones modulate both the reactivity[18] and the structure[19] of the vascular system. In the present study, the sexual dimorphism was unaffected by the coexistence of diabetes melli-

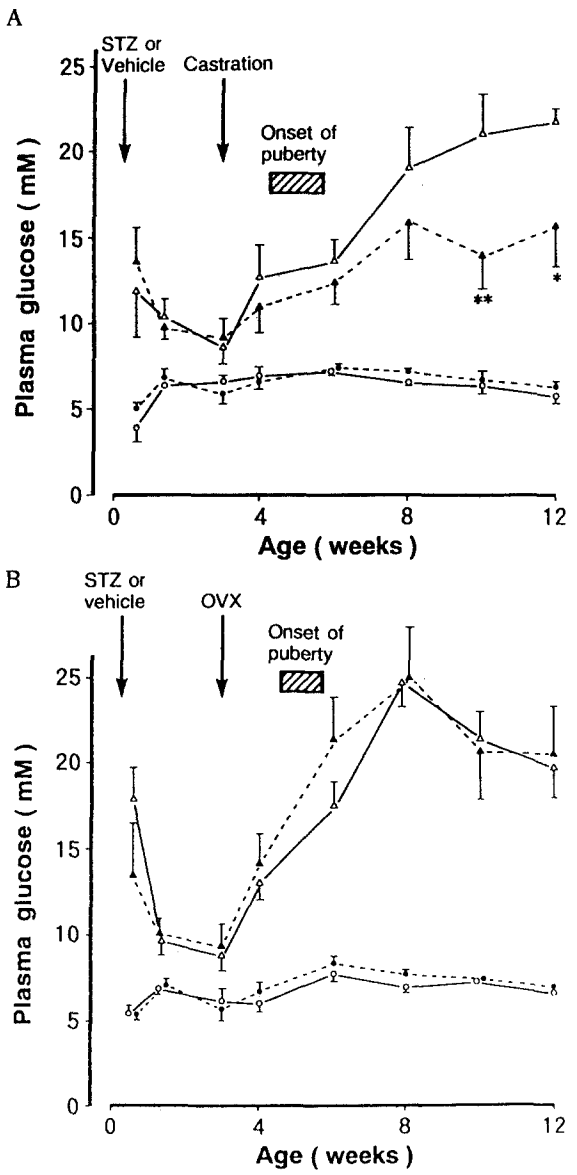

Fig 3. Changes in nonfasting plasma glucose levels for intact and gonadectomized SHR treated neonatally with STZ (△ and ▲, respectively) or vehicle alone (○ and ●, respectively). (A) Males; (B) females. *$P < .05$, **$P < .01$: *v* intact STZ-treated SHR.

tus. However, it remains to be determined whether the effect of gonadectomy might be due to either the increased gonadotropins or the decreased peripheral sex steroids. Thus, it is necessary that gonadectomized animals be substituted with androgens to evaluate the effects of androgens on blood pressure and glycemia.

It is well known that orchidectomy in immature male rats leads to growth retardation, whereas ovariectomy in immature female rats leads to weight gain.[20] However, in the present study, body weight gain was reduced by orchidectomy in vehicle-treated SHR but not in STZ-treated SHR. This is probably because of the improved metabolic control induced by orchidectomy in STZ-treated SHR, or because the anabolic action of testosterone had been weakened by hypoinsulinemia in the diabetic state. By contrast, the growth-promoting effect of ovariectomy was unaffected by the coexisting diabetes mellitus. This is consistent with findings reported by Dudley et al,[21] who showed that body weight changes were normal in response to estradiol replacement and withdrawal in ovariectomized STZ-induced diabetic rats. This suggests that insulin and ovarian hormones may regulate body weight via separate pathways.

The effects of gonadectomy on animal diabetes vary by animal models. Orchidectomy ameliorated diabetes induced by subtotal pancreatectomy,[22] single STZ injection,[23] multiple low-dose STZ injection,[24] and encephalomyocarditis virus infection.[25] In addition, ovariectomy increased the incidence of diabetes in subtotally pancreatectomized rats.[22] By contrast, the incidence of diabetes was increased by orchidectomy and decreased by ovariectomy in non-obese diabetic mice.[26] Gonadectomy had no effect on glucose tolerance in genetically obese rats, namely Wistar diabetic fatty rats and Zucker rats.[27] In the neonatal STZ-diabetes model, STZ destroys pancreatic β cells and hyperglycemia develops. Later, a recovery from hyperglycemia occurs because neonatal β cells are able to regenerate. However, this β-cell regeneration is incomplete and the β-cell mass is still reduced in comparison to nondiabetic controls. Subse-

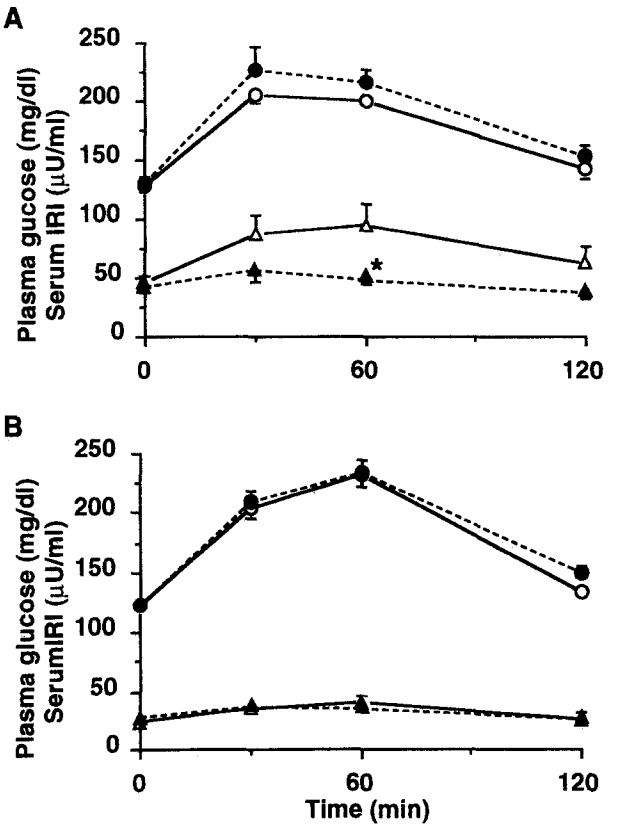

Fig 4. Oral glucose tolerance test (2 g/kg body weight) for intact (plasma glucose, ○; serum IRI, △) and gonadectomized (plasma glucose, ●; serum IRI, ▲) nondiabetic SHR. (A) Males; (B) females. *$P < .05$ *v* intact SHR.

Table 1. Characteristics of 12-Week-Old Intact or Orchidectomized SHR Treated With Vehicle or STZ at 2 Days of Age

Characteristic	Vehicle		STZ	
	Intact	Castrated	Intact	Castrated
No. of animals	5	5	6	8
Free testosterone (pmol/L)	155.0 ± 99.5	2.1 ± 0.7†	54.4 ± 24.6	1.4 ± 0.3‡
Estradiol (pmol/L)	68 ± 3	159 ± 20†	98 ± 22	125 ± 15
Food intake (g/d)	20.9 ± 0.8	17.4 ± 1.6	24.0 ± 2.4	19.9 ± 1.5
Urinary glucose (g/d)	0	0	5.2 ± 1.1‖	2.6 ± 0.7*§
Overnight fast				
Plasma glucose (mmol/L)	7.1 ± 0.3	7.2 ± 0.3	6.9 ± 0.6	7.4 ± 0.5
Serum IRI (pmol/L)	348 ± 78	258 ± 48	366 ± 90	210 ± 18
Pancreatic IRI content (U/g)	2.89 ± 0.17	2.91 ± 0.10	0.29 ± 0.09‖	0.29 ± 0.05‖
Total cholesterol (mmol/L)	1.32 ± 0.13	1.40 ± 0.10	1.55 ± 0.05	1.81 ± 0.13

NOTE. Values are the mean ± SEM.
*$P < .05$, †$P < .01$, ‡$P < .001$: *v* corresponding intact group.
§$P < .05$, ‖$P < .001$: *v* corresponding vehicle-treated group.

Table 2. Characteristics of 12-Week-Old Intact or Ovariectomized SHR Treated With Vehicle or STZ at 2 Days of Age

Characteristic	Vehicle		STZ	
	Intact	Ovariectomized	Intact	Ovariectomized
No. of animals	5	5	11	7
Free testosterone (pmol/L)	10.1 ± 5.5	1.4 ± 0.7*	4.2 ± 1.4	0.7 ± 0.3*
Estradiol (pmol/L)	467 ± 115	129 ± 14‡	301 ± 23‖	120 ± 15†
Food intake (g/d)	17.6 ± 0.9	17.4 ± 0.8	21.4 ± 1.2	21.7 ± 1.9
Urinary glucose (g/d)	0	0	3.8 ± 0.6¶	4.4 ± 0.8¶
Overnight fast				
Plasma glucose (mmol/L)	6.8 ± 0.2	6.8 ± 0.2	7.2 ± 0.4	7.2 ± 0.6
Serum IRI (pmol/L)	144 ± 12	174 ± 24	324 ± 30§	360 ± 72§
Pancreatic IRI content (U/g)	2.50 ± 0.17	2.24 ± 0.24	0.41 ± 0.10¶	0.25 ± 0.07¶
Total cholesterol (mmol/L)	1.45 ± 0.10	2.17 ± 0.13‡	1.78 ± 0.08§	2.64 ± 0.08‡‖

NOTE. Values are the mean ± SEM.
*$P < .05$, †$P < .01$, ‡$P < .001$: *v* corresponding intact group.
§$P < .05$, ‖$P < .01$, ¶$P < .001$: *v* corresponding vehicle-treated group.

Table 3. Kidney Weight and Urinary Albumin Excretion in Intact or Orchidectomized SHR Treated Neonatally With Vehicle or STZ

Parameter	Vehicle		STZ	
	Intact	Castrated	Intact	Castrated
Body weight (g)	264 ± 6	245 ± 6‡	213 ± 10‖	224 ± 9
Kidney weight (% body weight)	0.37 ± 0.01	0.31 ± 0.01*	0.53 ± 0.02‖	0.38 ± 0.02‡§
Urinary albumin excretion (μg/d)	1,528 ± 296	460 ± 69†	4,745 ± 1,233§	1,396 ± 181‡‖

NOTE. Values are the mean ± SEM.
*$P < .05$, †$P < .01$, ‡$P < .001$: *v* corresponding intact group.
§$P < .01$, ‖$P < .001$: *v* corresponding vehicle-treated group.

Table 4. Kidney Weight and Urinary Albumin Excretion in Intact or Ovariectomized SHR Treated Neonatally With Vehicle or STZ

Parameter	Vehicle		STZ	
	Intact	Ovariectomized	Intact	Ovariectomized
Body weight (g)	187 ± 3	212 ± 1*	175 ± 9	195 ± 6*
Kidney weight (% body weight)	0.39 ± 0.01	0.33 ± 0.01	0.47 ± 0.02†	0.48 ± 0.03§
Urinary albumin excretion (μg/d)	96 ± 6	106 ± 24	285 ± 38§	253 ± 51‡

NOTE. Values are the mean ± SEM.
*$P < .05$ *v* corresponding intact group.
†$P < .05$, ‡$P < .01$, §$P < .001$: *v* corresponding vehicle-treated group.

quently, hyperglycemia gradually develops as the rats grow.[28,29] The changes in pancreatic IRI content after STZ insult showed that the initial reduction and the following regeneration of neonatal β cells did not differ between male and female SHR. We previously reported that female SHR developed overt hyperglycemia earlier than male SHR at 6 weeks of age.[30] This sex difference in the developmental pattern of hyperglycemia was not affected by gonadectomy. However, orchidectomy ameliorated the development of hyperglycemia after the onset of puberty in male STZ-treated SHR without the increase in pancreatic IRI content. Although the mechanisms could not be explained from the present results, orchidectomy might improve insulin sensitivity in SHR, because serum insulin in an oral glucose tolerance test was decreased by orchidectomy in vehicle-treated SHR despite the similar glycemic levels. This improved insulin sensitivity may also contribute in part to the amelioration of hypertension in SHR. The role of sex hormones in the pathogenesis of hypertension and diabetes remains to be determined in humans.

Diabetic microangiopathy rarely occurs before puberty, which suggests that changes in sex hormones may influence the development of this condition.[31] In STZ-induced diabetic rats, STZ treatment at 13 weeks of age (after the onset of puberty) produced renal enlargement, whereas such treatment at 5 weeks of age (before the onset of puberty) did not change kidney weight.[32] Blantz et al[13] reported that androgen administration in ovariectomized rats induced renal hypertrophy and an increase in the single nephron glomerular filtration rate. Furthermore, Williamson et al[33] reported that orchidectomy reduced the diabetes-induced increase in vascular permeability of various types of tissue, including the kidneys. They also showed that orchidectomy was associated with a reduction in polyol pathway abnormalities and collagen cross-linking. Therefore, the orchidectomy-induced reduction of kidney weight and albuminuria in diabetic SHR may be induced not only by an amelioration of hypertension and diabetes mellitus, but also by the direct effects of testosterone deficiency on the kidneys.

In conclusion, SHR given STZ during the neonatal period developed genetic hypertension and overt hyperglycemia after the onset of puberty and had increased kidney weight and urinary albumin excretion in adulthood in both males and females. Gonadectomy before puberty had protective effects against the development of hypertension, hyperglycemia, nephromegaly, and albuminuria in males but not in females. This suggests that sex hormones may be important as a link between diabetes mellitus and hypertension in males.

ACKNOWLEDGMENT

We are grateful to Junko Ishimatsu and Kayoko Sekioka for technical assistance, and we are also indebted to Dr Seizo Sadoshima for providing us with SHR rats.

REFERENCES

1. Fuller JH: Epidemiology of hypertension associated with diabetes mellitus. Hypertension 7:3-7, 1985 (suppl 2)

2. Consensus Statement: Treatment of hypertension in diabetes. Diabetes Care 16:1394-1401, 1993

3. Landon J, Wynn V, Samols E: The effect of anabolic steroid on blood sugar and plasma insulin levels in man. Metabolism 12:924-935, 1963

4. Cohen JC, Hickman R: Insulin resistance and diminished glucose tolerance in powerlifters ingesting anabolic steroids. J Clin Endocrinol Metab 64:960-963, 1987

5. Beck P: Contraceptive steroids. Modifications of carbohydrate and lipid metabolism. Metabolism 22:841-855, 1973

6. Björntorp P: Hyperandrogenicity in women. A prediabetic condition? J Intern Med 234:579-583, 1993

7. Lindstedt G, Lundberg P-A, Lapidus L, et al: Low sex-hormone–binding globulin concentration as independent risk factor for development of NIDDM. 12-yr follow-up of population study of women in Gothenburg, Sweden. Diabetes 40:123-128, 1991

8. Haffner SM, Valdez RA, Morales PA, et al: Decreased sex hormone–binding globulin predicts noninsulin-dependent diabetes mellitus in women but not in men. J Clin Endocrinol Metab 77:56-60, 1993

9. Ferrannini E, Buzzigoli G, Bonadonna R, et al: Insulin resistance in essential hypertension. N Engl J Med 317:350-357, 1987

10. Reaven GM: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

11. Mondon CE, Reaven GM: Evidence of abnormalities of insulin metabolism in rats with spontaneous hypertension. Metabolism 37:303-305, 1988

12. Iwase M, Kikuchi M, Nunoi K, et al: A new model of type 2 (non–insulin-dependent) diabetes mellitus in spontaneously hypertensive rats. Diabetes induced by neonatal streptozotocin treatment. Diabetologia 29:808-811, 1986

13. Blantz RC, Peterson OW, Blantz ER, et al: Sexual differences in glomerular ultrafiltration. Effect of androgen administration in ovariectomized rats. Endocrinology 122:767-773, 1988

14. Wakisaka M, Nunoi K, Iwase M, et al: Early development of nephropathy in a new model of spontaneously hypertensive rat with non–insulin-dependent diabetes mellitus. Diabetologia 31:291-296, 1988

15. Conover WJ, Iman RL: Rank transformations as a bridge between parametric and nonparametric statistics. Am Statist 35:124-133, 1981

16. Iams SG, Wexler BC: Inhibition of the development of spontaneous hypertension in SH rats by gonadectomy or estradiol. J Lab Clin Med 94:608-616, 1979

17. Chen Y-F, Meng Q-C: Sexual dimorphism of blood pressure in spontaneously hypertensive rats is androgen dependent. Life Sci 48:85-96, 1991

18. McConnaughey MM, Iams SG: Sex hormones change adrenoceptors in blood vessels of the spontaneously hypertensive rat. Clin Exp Hypertens 15:153-170, 1993

19. Fischer GM, Swain ML: Effect of sex hormones on blood pressure and vascular connective tissue in castrated and noncastrated male rats. Am J Physiol 232:H617-H621, 1977

20. Wade GN, Gray JM: Gonadal effects on food intake and adiposity. A metabolic hypothesis. Physiol Behav 22:583-593, 1979

21. Dudley SD, Gentry RT, Silverman BS, et al: Estradiol and insulin. Independent effects on eating and body weight in rats. Physiol Behav 22:63-67, 1979

22. Houssay BA: Action of sex hormones on experimental diabetes. Br Med J 1:505-510, 1951

23. Maclaren NK, Neufeld M, McLaughlin JV, et al: Androgen sensitization of streptozotocin-induced diabetes in mice. Diabetes 29:710-716, 1980

24. Rossini AA, Williams RM, Appel MC, et al: Sex differences in the multiple-dose streptozotocin model of diabetes, Endocrinology 103:1518-1520, 1978

25. Boucher DW, Hayashi K, Rosenthal J, et al: Virus-induced diabetes mellitus. III. Influence of the sex and strain of the host. J Infect Dis 131:462-466, 1975

26. Makino S, Kunimoto K, Muraoka Y, et al: Effect of castration on the appearance of diabetes in NOD mouse. Exp Anim 30:137-140, 1981

27. Kava RA, West DB, Lukasik VA, et al: The effects of gonadectomy on glucose tolerance of genetically obese (fa/fa) rats. Influence of sex and genetic background. Int J Obes 16:103-111, 1992

28. Portha B, Picon L, Rosselin G: Chemical diabetes in the adult rat as the spontaneous evolution of neonatal diabetes. Diabetologia 17:371-377, 1979

29. Bonner-Weir S, Trent DF, Honey RN, et al: Responses of neonatal rat islets to streptozotocin. Limited β-cell regeneration and hyperglycemia. Diabetes 30:64-69, 1981

30. Iwase M, Kikuchi M, Nunoi K, et al: Sex differences in diabetes induced by neonatal streptozotocin treatment in spontaneously hypertensive rats. Diabetes Res Clin Pract 4:61-65, 1987

31. Sosenko JM, Miettinen OS, Williamson JR, et al: Muscle capillary basement-membrane thickness and long-term glycemia in type 1 diabetes mellitus. N Engl J Med 311:694-698, 1984

32. Bach LA, Jerums G: Effect of puberty on initial kidney growth and rise in kidney IGF-1 in diabetic rats. Diabetes 39:557-562, 1990

33, Williamson JR, Rowold E, Chang K, et al: Sex steroid dependency of diabetes-induced changes in polyol metabolism, vascular permeability, and collagen cross-linking. Diabetes 35:20-27, 1986