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Mechanisms of Hyperkalemia Associated with Hyporeninemic Hypoaldosteronism in Streptozotocin-Induced Diabetic Rats

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This study was aimed at investigating the mechanisms of clinically important overt hyperkalemia in diabetes mellitus with underlying hyporeninemic hypoaldosteronism known as a classic model of the syndrome of hyporeninemic hypoaldosteronism (SHH). Rats (Sprague-Dawley, male) were streptozotocin-treated (60 mg/kg, ip) and used after 60 days. Rats with plasma glucose levels higher than 300 mg/dL (mean±SEM, 423±20 mg/dL, n=8) were selected as the diabetic group. Age-matched normal rats served as control (mean plasma glucose, 88±2, mg/dL, n=8). Serum potassium concentrations and osmolalities as well as serum creatinine levels were significantly higher in the diabetic than in the control group (5.07±0.09 vs 4.68±0.11 mEq/L; 330±14 vs 290±3 mOsm/L; 0.40±0.03 vs 0.31±0.02 mg/dL, $p<0.05$). Plasma renin activity (PRA) in the diabetic group was significantly lower than that in the control group (6.0±1.0 vs 12.1±1.1 ng AI/ml/h, $p<0.001$). Plasma aldosterone concentration (PAC) was also significantly lower in the former than in the latter (368±30 vs 761±57 pg/ml, $p<0.001$). Renomegaly, abnormal distal tubular cells with few organelles, and increased lipid droplets with pyknotic nucleus in zona glomerulosa of the adrenal glands were noted in the diabetic group. In conclusion, multifactorial causes including insulinopenia, hyperosmolality, elevated serum creatinine level and hypoaldosteronism with possible contribution of altered distal tubular response to aldosterone may have interacted to develop hyperkalemia in these diabetic rats.

Key Words : *Hyperkalemia, Diabetes Mellitus, Hyporeninemic Hypoaldosteronism, Streptozotocin.*

INTRODUCTION

Following the first description of a patient with selective aldosterone deficiency in 1957 (Hudson JB et al., 1957) and the series of patients manifesting what is now recognized as the associated syndrome in 1964 (Carroll HJ et al., 1964), the syndrome of hyporeninemic hypoaldosteronism (SHH) has become widely appreciated in the past two decades. More than half of the patients with SHH had diabetic nephropathy (Schamberlan M et al., 1972, Christlieb AR., 1974, Deleiva A et al., 1976, Perez GO et al., 1977, DeFronzo RA, 1980).

Both insulin and aldosterone having vital roles in cellular potassium uptake and renal potassium excretion, respectively, have long been known to influence potassium homeostasis (Cox et al., 1978), and a deficiency of both hormones in diabetes with SHH may easily predispose to hyperkalemia (Goldfarb S et al., 1976). Therefore, it has been frequently reported that, particularly, diabetes with selective

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hypoaldosteronism (SHH) would be the important clinical setting for the deranged potassium metabolism.

On the surface, deficiency of aldosterone and lack of insulin in SHH with diabetes are the principal reasons for the development of hyperkalemia, but may not be sufficient to account for it. Clinically, a partial deficiency of both hormones commonly seen in SHH does not cause hyperkalemia and diabetics with deficiencies of renin and aldosterone comparable to those seen in SHH may have normal potassium concentrations (Perez Go et al., 1977). The major question is, "why does spontaneous hyperkalemia fail to develop in some patients who have significant decreases in plasma renin activity and plasma aldosterone levels?" The answers for this would be that the hyperkalemia frequently present in diabetic patients with insulin or aldosterone deficiency (or both) seemed to be the result of a complex interplay or other initiating events related to derangements in the potassium homeostasis, besides lack of insulin and aldosterone. In theory, such disturbances in clinical setting would be the reduction of glomerular filtration rate commonly accompanied in SHH, the decreased sodium delivery to the distal nephron related to reduced sodium intake, gastrointestinal salt loss, heart failure, or drugs interfering with the renin-angiotensin-aldosterone axis (e.g., indomethacin, heparin) or with renal blood flow (Ponce SP et al., 1985, Phelps KR et al., 1980, Tan SY et al., 1979).

Another suggestion has been made that a defect in tubular responsiveness to aldosterone, either independent of or in concert with insulin or aldosterone deficiency, may also play some role, because hyperkalemia may not be corrected with the usual dose of mineralocorticoid replacement in SHH (DeFronzo RA, 1980). However, the interrelationship of these multiple factors to develop overt hyperkalemia in diabetics with SHH has not been well defined so far (Phelps KR et al., 1980). Therefore, it seems to be important to define these initiating multiple factors involved in the development of hyperkalemia in the setting of diabetes with SHH.

In this study, the initiating mechanisms of overt hyperkalemia in diabetes with SHH were investigated in streptozotocin (STZ)-induced diabetic rats well known as an animal model for understanding the pathophysiology of diabetes with hyporeninemic hypoaldosteronism, since their hormonal changes were consistent with those found in diabetic patients (Hayashi T et al., 1984 ; Kigoshi et al., 1986 ; Phelps KR et al., 1980 ; Schambelan et al., 1979). Also, another purpose of this investigation was to look for the ultrastructural changes of both renal distal tubular cells known as major target tissues of the hormonal action of aldosterone in kidney and zona glomerulosa cells of adrenal glands where synthesis or release of aldosterone occurs mainly. So far, there have been sparse or isolated morphological reports of either the zona glomerulosa of adrenal gland (Rebuffat P et al., 1988) or renal tubular cells (Rasch R, 1984) in STZ-induced experimental diabetic rats.

MATERIALS AND METHODS

Animal treatments and general procedures

Age and body weight (200 gm) matched Sprague-Dawley male rats were given a single ip injection of streptozotocin (STZ), 60 mg/kg, in 1mM citrate buffer, pH 4 to produce nonketotic diabetes and maintained for 60 days on standard chow diet and water *ad libitum*. Tail bleedings were performed once every other day to monitor blood glucose levels with chemistrips (Glucometer, Miles, U.S.A). One week after injection of STZ, rats with steady blood glucose levels higher than 300 mg/dL were used as STZ-induced diabetic rats (n=8). The normal control rats (n=8) were treated the same as the STZ-induced diabetic rats except for injections of an equal volume of 0.9% saline in 1 mM citrate buffer, pH 4.

One week prior to killing, two consecutive 24-hr urines for biochemical analysis were obtained from the diabetic and control rats kept in metabolic cages. Blood samples were collected by decapitation at 60 days. Blood and urine chemistries were performed, and electrolytes were measured by the automated bichromatic analysis system using ion selective electrode (Hitachi 736-20), and plasma osmolality was measured by freezing point depression (Model 3D Ⅱ, Advanced Instruments, INC., Massachusetts, U.S.A.). Plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were estimated by standard radioimmunoassay (Diagnostic products Co. Los Angeles, U.S.A.).

Ultrastructural examination

Adrenal glands and kidneys were promptly removed. Kidney and adrenal tissue for electron mic-

roscopy were cut into 1-2mm slices with razor blades. Sliced pieces of the adrenals and kindeys were fixed in 2.5% glutaraldehyde in 0.1M cacodylate buffer (pH 7.4), and post fixation for 2h in 1% osmium in 0.1M cacodylate buffer followed. Fixed tissues were dehydrated and embedded in Epon 812. Thick sections were cut and stained with toluidine blue to permit random selection of the zona glomerulosa and distal tubules in the block, respectively. Ultra-thin sections were obtained on a Sorvall MT-4000 ultramicrotome with a diamond knife, pláced on Formvar-coated one-hole grids, stained with uranyl acetate and lead citrate, and examined with a Hitachi HU-12 electron microscope.

Statistical analysis

Differences between STZ-induced rats and control rats were evaluated using Student's non-paired or paired *t* tests as appropriate and p value less than 0.05 was considered statistically significant. This statistical work was performed by Stat-Works (Macintosh®) software. Results were expressed as mean±SEM.

RESULTS

General characteristics of control and STZ-induced diabetic rats (Table 1)

STZ-diabetic rats developed blood glucose concentrations almost five times higher than that of control rats (423±20 vs. 88±2 mg/dL). These diabetic rats had significantly lower body weights (293±4 vs. 340±7 gm, $p<0.001$), but heavier kidney weights compared with those of control rats (1.22±0.03 vs. 1.05±0.06 gm, $p<0.001$). Urine volumes were two and half times greater for diabetic rats than for control rats and significant glucosuria in diabetic rats was observed as compared with that in control rats. Also, diabetic rats showed a substantial increase in urinary sodium and potassium excretion as compared with control rats.

Peripheral blood measurements (Fig. 1 and Fig. 2)

In diabetic rats at 60 days following injection of STZ revealed significantly lower levels of PRA as

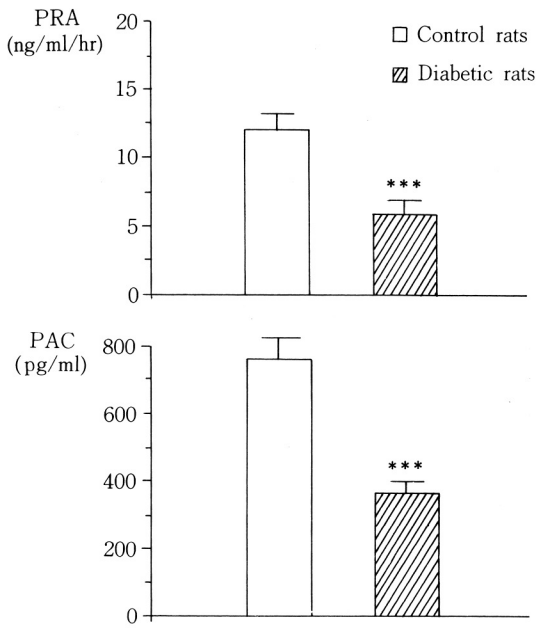

Fig. 1. Plasma renin activity (PRA) and plasma aldosterone concentration (PAC) in normal control and STZ-induced diabctic rats. (***$p<0.001$)

Table 1. Baseline general characteristics of normal control and STZ-induced diabetic rats

	Control rats (n=8)	Diabetic rats (n=8)
Bl. Glucose (mg/dL)	88±2	423±20***
B.W. (gm)	340±7	293±4***
K.W. (gm)	1.05±0.06	1.22±0.03***
Urine Vol. (ml/24 h)	13.8±1.5	31.4±7.0*
Urine Glu. (mg/24 h)	1.3±0.4	761±173***
Urine Na (mEq/24 h)	1.1±0.1	1.6±0.2*
Urine K (mEq/24 h)	1.1±0.1	2.0±0.3**

Bl, blood ; B.W., body weight ; K.W., kidney weight ; Vol, volume ; Glu. glucose ; Na, sodium ; K, potassium.
*$p<0.05$ vs. corresponding values for control rats. **$p<0.01$, ***$p<0.001$.

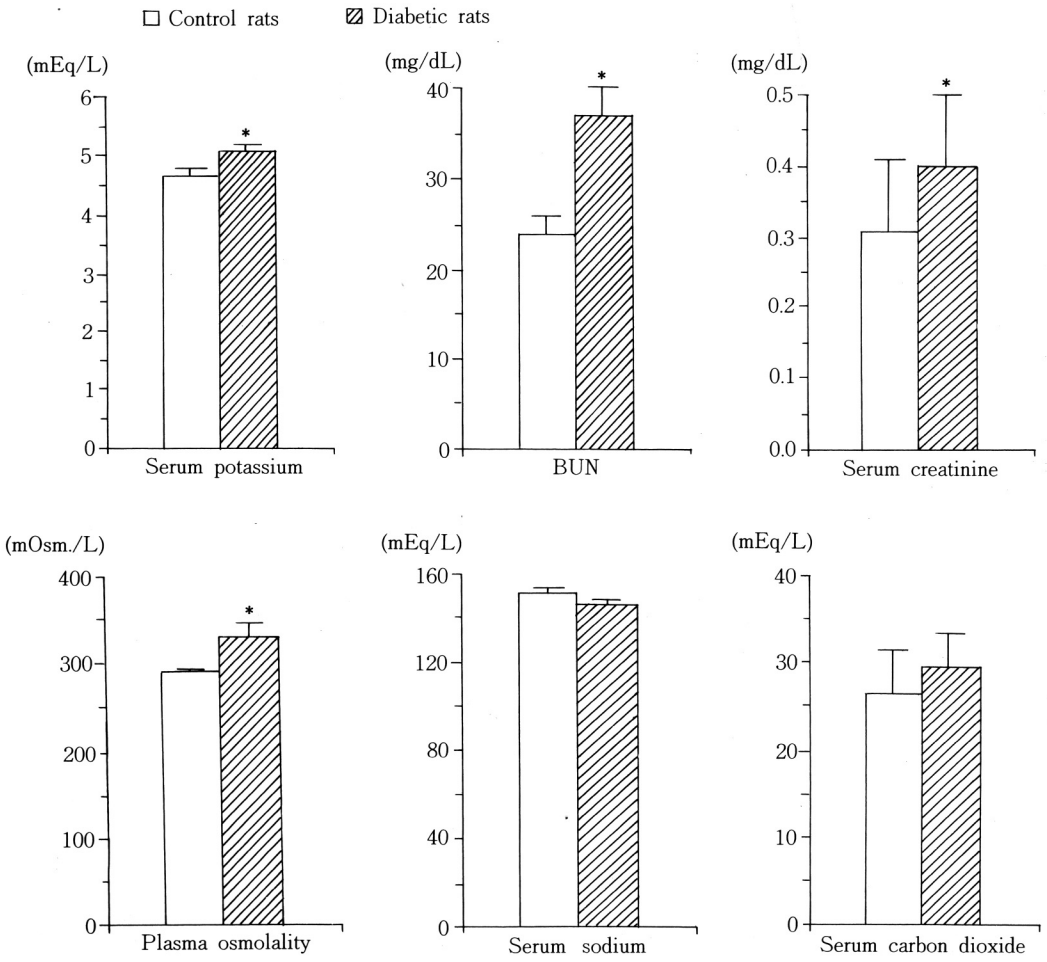

Fig. 2. Serum levels of potassium, BUN, creatinine, sodium, carbon dioxide, and plasma osmolality in normal control and STZ-induced diabetic rats. (*$p<0.05$)

well as PAC when compared with normal control rats (PRA, 6.0±1.0 vs. 12.1±1.1 ng AI/ml/hr, $p<0.001$; PAC, 368±30 vs. 761±57 pg/ml, $p<0.001$). The reduction in percentage of PRC and PAC of diabetic rats in comparison with control rats reached about 50%, respectively (Fig. 1). As shown in Fig. 2, the serum potassium concentration was increased in diabetic rats to 5.07±0.09 mEq/L compared with 4.68±0.11 mEq/L for normal control rats ($p<0.05$). There were significant elevations in BUN (37±4 vs. 24±2 mg/dL, $p<0.05$), serum creatinine (0.40±0.03 vs. 0.31±0.02 mg/dL, $p<0.05$) and plasma osmolality (330±14 vs. 290±3 mOsm/L, $p<0.05$), but not in concentration of serum sodium and carbon dioxide (CO_2) for diabetic rats.

Ultrastructural morphology of distal tubular and zona glomerulosa cells in control and diabetic rats (Fig. 3, 4, 5 and 6)

Though the figures are not shown in this paper, a somewhat mild increase and rare myeloid bodies in the glomerular mesangial matrix were the only findings of glomerular abnormality in STZ induced diabetic rats.

A number of mitochondrias and extensive basal infoldings of the cell membrane of normal distal

tubular cells were observed (Fig. 3). At two months post-induction of diabetes, distal tubular cells of STZ-induced diabetic rats had few mirovilli on luminal cell membrane with strikingly decreased basal

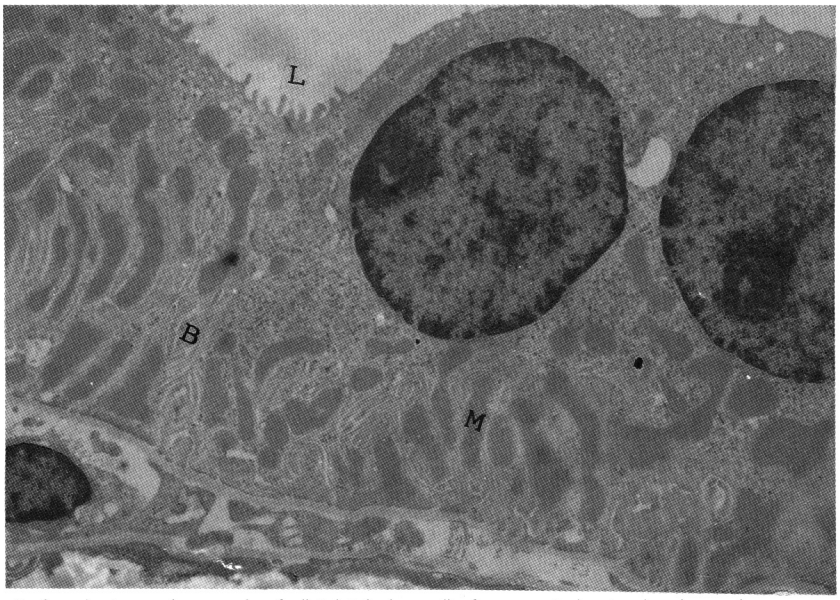

Fig. 3. An electron micrograph of distal tubular cells from control rats showing a large amout of slender mitochondria (M) along the deep infoldings of the basal laminae (B). Lumen (L) with microvilli is seen. Magnification × 14,000.

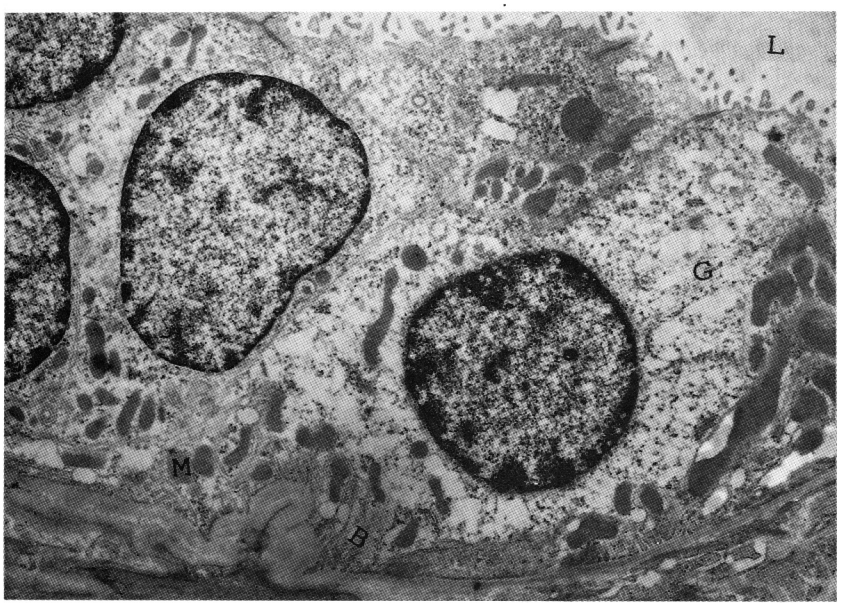

Fig. 4. An electron micrograph of distal tubular cells in STZ-induced diabetic rats, two months after onset of diabetes. The amount of mitochondria (M) and the basal infoldings (B) are very sparse. The cytoplasm is filled with granules (G) resembling glycogen-like particles. Toward the lumen (L) few microvilli are seen, Magnification × 10,500.

infoldings and mitochondrias. The cytoplasm of these abnormal cells contained notably few organelles and was loaded with large diffusely distributed granules (Fig. 4). These abnormal tubules were located in the cortex and in the outer stripe of the outer medulla. Abnormal cells have neither been

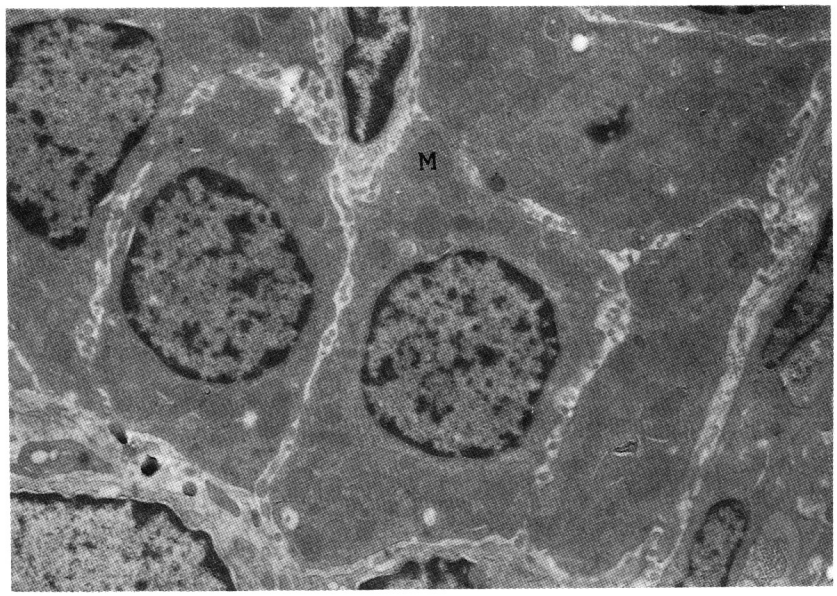

Fig. 5. An electron micrograph of zona glomerulosa cells of control rats showing round or elongated mitochondrias (M). Magnification × 10,500.

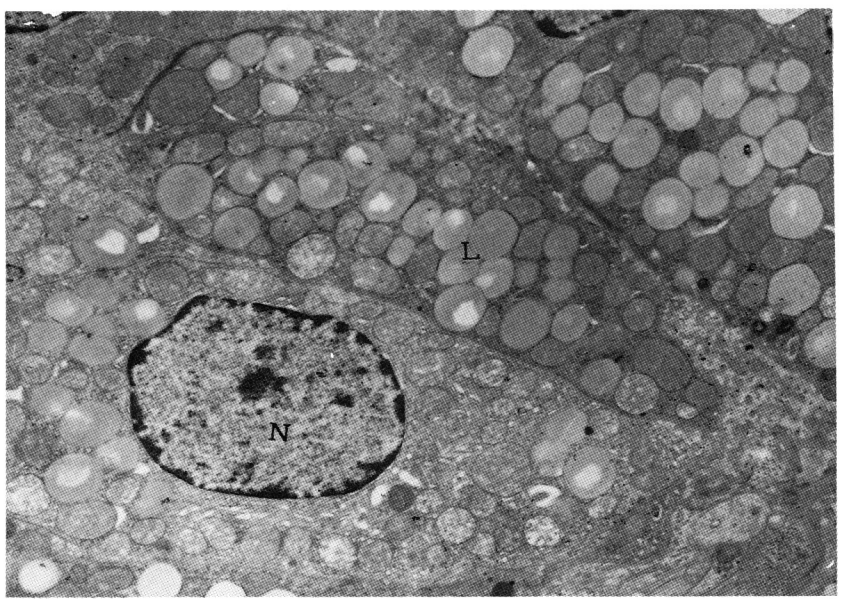

Fig. 6. An electron micrograph of zona glomerulosa cell in STZ-induced diabetic rats, two months after onset of diabetes. A striking increase in the number of lipid droplets (L) and a decrease in the number of mitochondria (M) with pyknotic nucleus (N) were noted. Magnification × 12,000.

observed in profiles containing proximal tubular cells nor in connection with cells of collecting ducts.

Zona glomerulosa cells of control rats were filled with round mitochondria and smooth endoplasmic reticulum (Fig. 5). Electron microscopic alterations of zona glomerulosa cells in STZ-induced diabetic rats were an apparent increase in the number of lipid droplets associated with somewhat decreased numbers of mitochondria and pyknotic nucleus (Fig. 6).

DISCUSSION

In this study, reduced secretion of renin and aldosterone as well as hyperkalemia (SHH) was observed in the STZ-induced diabetic rats about 60 days after the induction of diabetes.

The previously proposed explanations of the pathogenetic mechanisms of the hyporeninemia of SHH include damage to juxtaglomerular apparatus (Schindler AM et al., 1966), impaired conversion of precursors of renin to the active hormone (Deleiva A et al., 1976), insufficient sympathetic stimulation of renin producing cells (Hedeland H et al., 1969), inhibition of renin release by hyperkalemia (Vander AJ, 1970), physiologic suppression of renin release by volume expansion (Oh MS et al., 1974), and altered synthesis of renal prostaglandins (Tan SY et al., 1979). Since the first report suggesting that the aldosterone deficiency of SHH under consideration is a secondary rather than a primary phenomenon (Schambelan M et al., 1972), hyporeninemia has been proposed as the only factor contributing to the hypoaldosteronemia of SHH. Alternatively, however, insulin lack in SHH of diabetics could directly effect aldosterone secretion by reducing cellular influx of potassium (Andres R et al., 1962 ; DeFronzo RA et al., 1978) or by affecting metabolism within the adrenal gland leading to impaired steroidogenesis in zona glomerulosa and the presence of possible independent aldosterone synthetic defect has been suggested (Deleiva A et al., 1976). So far, however, none of these arguments has been clearly validated. Also, the etiology of deficiency of both renin and aldosterone levels in STZ-induced diabetic rats still remains unknown from this study.

The notable drop in the basal plasma concentration of renin as well as aldosterone in the diabetic rats in this investigation was observed in accordance with previous investigations. But, the hyperkalemia observed in the present study in diabetic rats was not consistent with previous observations (Hayashi et al., 1984 ; Kigoshi et al., 1986, Rebuffat P et al., 1988). In addition to insulin and aldosterone deficiency in SHH, a number of other factors such as metabolic acidosis, hypertonicity, some degree of renal insufficiency, and exogenous drugs (e.g., ACE inhibitors, some beta blockers, nonsteroidal antiinflammatory agents, and potassium sparing diuretics) leading to alteration of the renin-angiotensin-aldosterone axis or the impairment in the renal tubular response to the aldosterone (Garella S et al., 1984 ; Walker BR et al., 1972) may contribute to hyperkalemia in diabetes. Metabolic acidosis (Adler S et al., 1977) as well as hypertonicity (Makoff DL et al., 1971) have been known to produce a redistribution of potassium from the intracellular to the extracellular fluid.

Among these factors, with no exposure to drugs except STZ and unlikely metabolic acidosis with no significant changes in serum carbon dioxide level, the diabetic rats in this study had higher serum creatinine level with hyperkalemia and SHH, which was not observed in previous studies (Hayashi et al., 1984 ; Kigoshi et al., 1986, Rebuffat P et al., 1988). This elevated serum creatinine level, besides the deficiency of both renin and aldosterone in the diabetic rats, might contribute to the development of hyperkalemia which was similarly noted in a previous study (Pratt JH et al., 1984). This mild but significantly higher level of serum creatinine would have accompanied distal tubular lesions contributing to resistance of the kaliuretic effect of aldosterone leading to hyperkalemia. As supportive evidence in the previous functional studies, the correction of hyperkalemia in diabetic patients often required very large doses of mineralocorticoids, and reduced tubular responsiveness thus became suspicious (DeFronzo RA, 1980).

Hyperglycemia may produce hyperkalemia in diabetic partients with either normal or deficient aldosterone release (Goldfarb et al., 1975 ; Goldfarb et al., 1976 ; Perez Go et al., 1977 ; Ammon AR, et al., 1978). However, in more recent studies, hyperosmolality induced with either hypertonic saline or glucose caused hyperkalemia equally in diabetic patients (Zerbe et al., 1979), and in patients with renal failure acute increase in blood osmolality by hypertonic NaCl was a cause of hyperkalemia independent of insulin levels (Conte G et al., 1990). This suggests that hyperosmolality may increase blood potassium levels even when insulin levels are normal. Therefore, the hyperosmolality itself observed in

the STZ-induced diabetic rats in this investigation seemed to play at least a partial role in the development of hyperkalemia in SHH.

As morphological evidence, in addition to the well known glomerular changes, interstitial scarring and tubular atrophy have been observed as the prominent features of diabetic nephropathy (Heptinstall RH, 1974). In the present study undertaken to locate the distal tubular lesion at the electron microscope level, the cytoplasm of the cells contained granules with strikingly few organelles and greatly reduced basal infoldings. These possibly glycogen like granules have been described in tubules in experimental diabetic rats in previous studies (Rasch R, 1984; Powel HC et al., 1979). The mechanism leading to glycogen accumulation in kidney tubules in experimental diabetes remains obscure. In distal tubular cells from normal rats, sodium-potassium-activated adenosine triphosphatase is localized in the cell membrane of the large and numerous basal infoldings, which are in close contact with the mitochondria. In the diabetic rats in this study, the basal infoldings as well as the mitochondrias of abnormal distal tubular cells were strikingly sparse, which implies abnormal sodium-potassium transport related to target tissue resistance of aldosterone in pathological cells. However, the exact role played by these distal tubular lesions with renal insufficiency in impaired potassium excretion is unclear at present.

With the above described morphological lesions of distal tubular cells of the kidney, the diabetic rats in this study also showed ultrastructural changes in the zona glomerulosa cells of the adrenal gland. A notable atrophy of adrenal zona glomerulosa has been known to be provoked by chronic renin suppression (Mazzocchi G et al., 1982). The findings in this study in the zona glomerulosa cells of diabetic rats-the decreased number of mitochondria with pyknotic nucleus, organelles actively involved in the aldosterone synthesis (Nussdorfer GG, 1986)-might be interpreted as the morphological evidence of the impaired aldosterone production. The lowered use of cholesterol in aldosterone synthesis may account for the notable rise in the volume of the lipid-droplet compartment observed in zona glomerulosa cells of STZ-induced diabetic rats (Rebuffat P et al., 1988). In fact, cholesterol is stored in the lipid droplets, quantity of which, at least in the rat, depends on the balance between exogenous uptake of cholesterol from serum high-density lipoproteins and its utilization in steroidogenesis (Nussdorfer GG, 1986; Andreis PG et al., 1990). Such a morphological change could contribute to lowering basal levels and subsequent responses of aldosterone production to a given stimulus.

In summary, 60 days after an injection of STZ, the diabetic rats developed hyporeninemic hypoaldosteronism accompanied by hyperkalemia (SHH) and were noted to have mild but significantly elevated serum creatinine level, hyperosmolality and ultrastructural alterations of distal tubular and zona glomerulosa cells as compared with normal control rats. From these findings it may conclude that, in addition to the lack of two hormones – insulin and aldosterone – in SHH of diabetics, elevated serum creatinine level with distal tubular lesions related to possibly tubular resistance, and the degree of hypertonicity might play roles in concert or individually in the development of the clinically important overt hyperkalemia in SHH of STZ-induced diabetic rats.

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