Int. J. Exp. Path. (1992) 73, 75–84

Rapid induction of glomerular lipidosis in APA hamsters by streptozotocin

Jin-Soo Han, Yoshinori Sugawara and Kunio Doi
Department of Biomedical Science, Faculty of Agriculture, The University of Tokyo, Bunkyo-ku, Tokyo 113, Japan

Received for publication 28 June 1991
Accepted for publication 20 September 1991

Summary. The pathology of male Syrian hamsters of APA strain which were injected intraperitoneally with 40 mg/kg body weight of streptozotocin (SZ) at 2 months of age was examined. It showed long-lasting prominent hyperglycaemia and hyperlipidaemia with glucosuria and the development of glomerular lipidosis from 1 month after SZ-injection (1 MAI). Glomerular lesions were restricted to the juxtamedullary cortex at 1 MAI and then extended to the subcapsular cortex. At 3 MAI, glomerular lesions were characterized by focal segmental glomerulosclerosis showing segmental expansion of the mesangial area due to an increase of basement membrane-like material and mesangial cells with lipid droplets and foam cells. SZ-induced diabetic APA hamsters will be a useful model for the investigation of glomerular lipidosis and focal segmental glomerulosclerosis.

Keywords: APA hamster, foam cell, focal segmental glomerulosclerosis, glomerular lipidosis

Syrian hamsters of the APA strain, which has been developed in Japan (Tajima 1968) and maintained as a closed colony by random breeding in our laboratory, are known to develop spontaneously from an early age mesangial thickening in the renal glomeruli (Han *et al.* 1992). They also develop focal and segmental glomerulosclerosis (FSG) after 6 months of age (Doi *et al.* 1987) instead of glomerular amyloidosis which is the most common renal lesion in aged Syrian hamsters of other strains (Mezza *et al.* 1984). In addition, Norimatsu *et al.* (1990) found spontaneous glomerular lipidosis closely related to hyperglycaemia and hyperlipidaemia in a 12-week-old male hamster of this strain. This suggested the possibility of developing a model of glomerular lipidosis by inducing hyperglycaemia and/or hyperlipidaemia in APA hamsters. Han *et al.* (1990) recently clarified the appropriate dose of streptozotocin (SZ) to induce hyperglycaemia with hyperlipidaemia in APA hamsters without nephrotoxicity.

Although some spontaneous and SZ-induced animal models have been used for studying diabetic nephropathy up to the present time, they need a very long time to induce renal lesions (Couser & Stilmant 1975; Gray *et al.* 1982; Mori *et al.* 1988; Shibata & Yasuda 1980; Wehner *et al.* 1972) and rarely demonstrate glomerular lipid deposition, one of the early changes observed in FSG (Diamond & Karnovsky 1988; Magil

Correspondence: J.-S. Han, Department of Biomedical Science, Faculty of Agriculture, The University of Tokyo, Bunkyo-ku, Tokyo 113, Japan.

& Cohen 1989). We therefore tried to induce glomerular lipidosis and subsequent FSG in APA hamsters by SZ within a shorter time period. This paper describes the histological and ultrastructural characteristics of renal lesions in APA hamsters up to 3 months after SZ-injection.

Materials and methods

Animals and treatment

Based on the results of previous study (Han *et al.* 1990), 20 2-month-old APA hamsters were injected intraperitoneally with 40 mg/kg body weight (b.w.) of SZ (Lot No. 78F-0517, Sigma) dissolved in 0.1 M citrate buffer (pH 4.5). Two out of 20 animals were excluded from the experiment at 1 day after injection (1 DAI) because their blood glucose levels failed to rise. Six age-matched male APA hamsters which were injected only with citrate buffer served as controls.

The animals were maintained under controlled conditions (temperature, 24 ± 1°C; relative humidity, 55 ± 5%) in plastic cages with sterilized wood shavings for bedding, and fed a commercial diet, CMF (Oriental Yeast Co. Ltd, Tokyo) and tap water *ad libitum* throughout the experimental period.

Body weight and food and water-intakes

Body weight and food and water-intakes per day were recorded at 2-week intervals throughout the experimental period.

Blood biochemistry

Blood samples collected after overnight fasting from the orbital sinus of each animal at 0, 1, 3, 5 and 7 DAI and subsequently at 2-week intervals were measured colorimetrically for serum glucose levels using Glucose C-test kit (Wako Pure Chemical Industries, Inc., Osaka).

Blood samples obtained after overnight fasting from six SZ-injected and two control animals at 3 MAI were also analysed by a Monarch autoanalyser (Instrumentation Laboratory, USA). The substances assayed were glucose (GLU), total protein (TP), total bilirubin (TBIL), triglyceride (TG), total cholesterol (TCHOL), β-lipoprotein (β LP), high density lipoprotein (HDL), phospholipid (PL), non-esterified fatty acids (NEFA), blood urea nitrogen (BUN), and creatinine (CRNN). Statistical analysis was performed using Student's *t*-test and values are expressed as mean $\pm$ s.d.

Urinalysis

Twenty-four-hour urine samples were collected using metabolic cages at 1, 2 and 3 MAI, and urinalysis was done using uropaper (Eiken Chemical Co., Tokyo).

Light microscopy

Six SZ-injected and two control animals were sacrificed by exsanguination under ether anaesthesia at 1, 2 and 3 months after injection (1, 2 and 3 MAI), respectively. Immediately after macroscopic examination, organs were fixed in 10% neutral buffered formalin, and 2 μm paraffin sections of the kidney were stained with haematoxylin and eosin (H&E), periodic acid–Schiff (PAS) or periodic acid–methenamine–silver (PAM) for light microscopic examinations. Paraffin sections, 4 μm thick, of other organs were stained with H&E. In addition, some sections of the pancreas were stained by avidin–biotin–peroxidase complex (ABC) method using Vectastain ABC kit (Vector Laboratories, Inc., USA) for the detection of insulin granules in the pancreatic islet β-cells. As a first antibody, anti-swine-insulin guinea-pig serum (Scandibodies Lab. Inc., Lakeside, CA) was employed. Frozen sections, 4 μm thick, of the spleen, liver and kidney were stained with Sudan black B (SBB) to reveal the presence of lipids.

Electron microscopy

For electron microscopic examination, small

pieces of the renal cortex obtained from each animal were fixed in 2.5% glutaraldehyde and 2.0% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4), post-fixed in 1.0% osmium tetroxide in the same buffer, and embedded in epoxy resin, Quetol 812 (Nisshin EM Co. Ltd, Tokyo). Ultrathin sections were double-stained with uranyl acetate and lead citrate, and observed under a JEM-1200EX electron microscope (JEOL Co. Ltd, Tokyo).

Results

Body weight and food and water-intakes

SZ-injected animals showed moderate b.w. loss during the first month but, thereafter, their b.ws tended to increase gradually (Fig. 1). SZ-injected animals exhibited marked increase in water and food-intakes within the first month and the elevated intakes continued throughout the experimental period (Fig. 2).

Blood biochemical findings

Eighteen of 20 SZ-injected hamsters showed prominent hyperglycaemia (> 320 mg/dl) at 1 DAI, and thereafter maintained high blood glucose levels (> 350 mg/dl) until killed as scheduled. On the other hand, control animals showed no elevation of blood glucose level throughout the experimental period.

At 3 MAI, all parameters examined showed higher values in SZ-injected animals than in controls. In particular, the levels of GLU, TBIL, PL, TP, and TCHOL contents in SZ-injected animals were significantly higher than those in controls (Table 1).

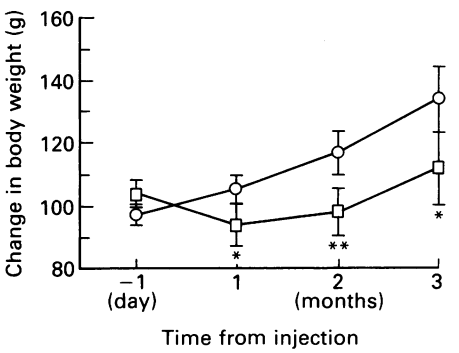


Fig. 1. Changes in body weight of APA hamsters. ○, C (Control group; $n=6$, 6, 4, and 2 at -1D and 1, 2, and 3 MAI, respectively); □, SZ (SZ-injected group; $n=6$ at each month). Values are mean ± s.d. $^{*}P \leqslant 0.05$; $^{**}P \leqslant 0.01$ (significantly different from controls).

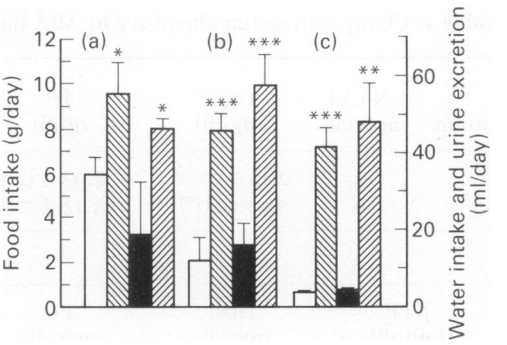


Fig. 2. a, Food and b, water intakes and c, urine excretion in APA hamsters. □, 1 MAI (C, $n=2$); ▨, 1 MAI (SZ, $n=6$); ■, 3 MAI (C, $n=2$); ▩, 3 MAI (SZ, $n=6$). Values are mean ± s.d. $^{*}P \leqslant 0.005$; $^{**}P \leqslant 0.01$; $P \leqslant 0.001$ (significantly different from controls).

Urinary findings

An increase in urinary excretion corresponding to that in water-intake was recorded in SZ-injected animals (Fig. 2). In addition, urine samples of SZ-injected animals were positive for protein (1 MAI: 12.4 mg/day; 3 MAI: 14.4 mg/day), glucose (500–2000 mg/dl) and ketone bodies (+ + +) on and after 1 MAI. Urine samples of control animals were positive for protein (1 MAI: 3.8 mg/day; 3 MAI: 4.4 mg/day) but not for other parameters.

Light microscopy of the kidney

At 1 MAI, mild focal expansion of the mesangial area and dilatation of capillary lumina were found in some glomeruli in the

Table 1. Changes in serum chemistry in APA hamsters at 3 MAI

Group	No. of animals	GLU (mg/dl)	TP (g/dl)	TBIL (mg/dl)	TG (mg/dl)	TCHOL (mg/dl)
C	2	226±7[a]	4.35±0.07	0.52±0.09	154±58	252±5
SZ	6	540±80**	13.18±7.79*	13.28±8.94*	4871±3058	1406±357**

β LP (mg/dl)	HDL (mg/dl)	PL (mg/dl)	NEFA (mEq/l)	BUN (mg/dl)	CRNN (mg/dl)
381±97.5	52±1.4	237.5±38.8	1.57±0.07	27.9±4.5	1.470±0.29
1492±625.7	57±9.1	1059.5±349.5*	5.19±2.00	45.8±18.8	1.475±0.07

[a] Mean±s.d.
*$P \leqslant 0.05$; **$P \leqslant 0.01$ (significantly different from controls).

juxtamedullary cortex. In addition, lipid droplets and foam cells were seen in the capillary lumen and/or expanded mesangial area of a few glomeruli. The number of glomeruli with lipid droplets and/or foam cells increased remarkably at 2 MAI.

At 3 MAI, such glomerular changes extended from the juxtamedullary cortex to the subcapsular cortex. These glomeruli had several foam cells, mainly in their expanded mesangial area (Fig. 3), and they were sometimes accompanied by lipid embolism (Fig. 4). Glomerular lesions were characterized by FSG showing segmental expansion of the mesangial area due to a marked increase in mesangial matrix and mesangial cells with lipid droplets and foam cells (Fig. 5). Partial adhesion of the affected segments to the Bowman's capsule was seen in some affected glomeruli. Moreover, irregular thickening of the basement membrane of Bowman's capsule and phagocytosis of lipid droplets by interstitial cells were common around the affected glomeruli. Lipids were also detected in some epithelial cells of the urinary tubules.

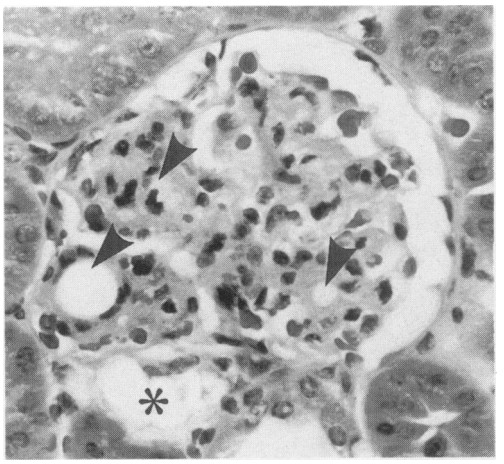
Intrarenal arteries and arterioles sometimes showed focal calcification and/or lipid infiltration in their tunica media. Swelling and vacuolization of epithelial cells were observed in some urinary tubules related to the affected glomeruli. Deposition of PAS-positive granules, which did not stain after diastase digestion, was detected in some epithelial cells of the distal urinary tubules with associated proteinaceous casts.

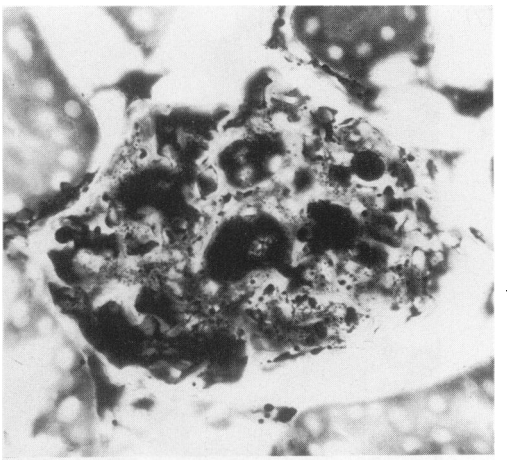
The kidneys of control animals showed similar but less marked expansion of the mesangial area and there was no lipid deposition (Fig. 6) in contrast to age-related SZ-injected animals.

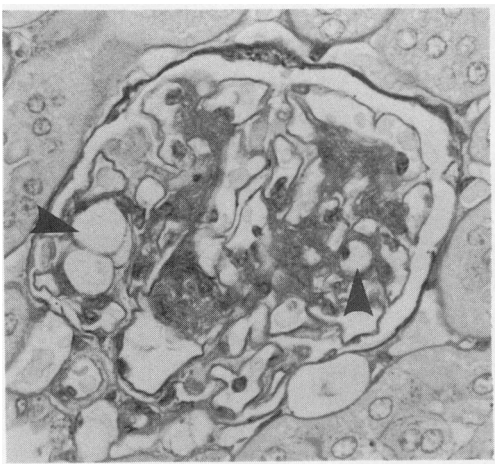
In organs other than the kidney, SZ-induced diabetic animals showed vacuolization and/or necrosis of β cells in the central area of atrophic pancreatic islets at 3 MAI, resulting in a marked loss of insulin-positive granules. In addition, prominent phagocytosis of lipids by reticular cells in the spleen and by Kupffer's cells in the liver, marked vacuolar degeneration of the adrenal medulla, and degeneration and atrophy of seminiferous tubules were frequently seen at 3 MAI.

Electron microscopy of renal glomeruli

At 1 MAI, changes such as segmental expansion of mesangial areas due to an increase of basement membrane-like material and mesangial cells with lipid deposition, slight







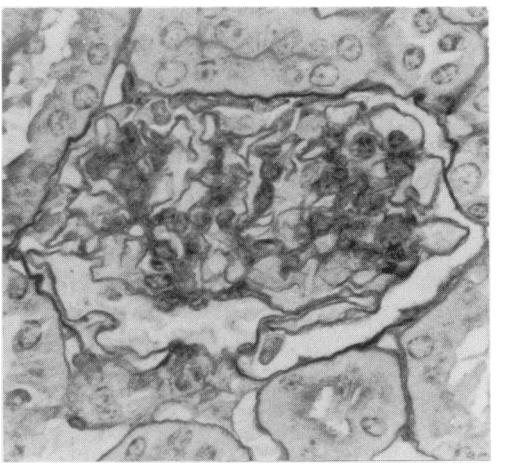


Fig. 3. Kidney of a SZ-injected APA hamster at 3 MAI Several vacuoles are seen in glomerular mesangium (arrowheads) and in interstitial space (asterisk). H&E. ×450.

Fig. 4. Kidney of a SZ-injected APA hamster at 3 MAI. Marked accumulation of lipids in glomerular capillary lumen and mesangium. SBB. ×360.

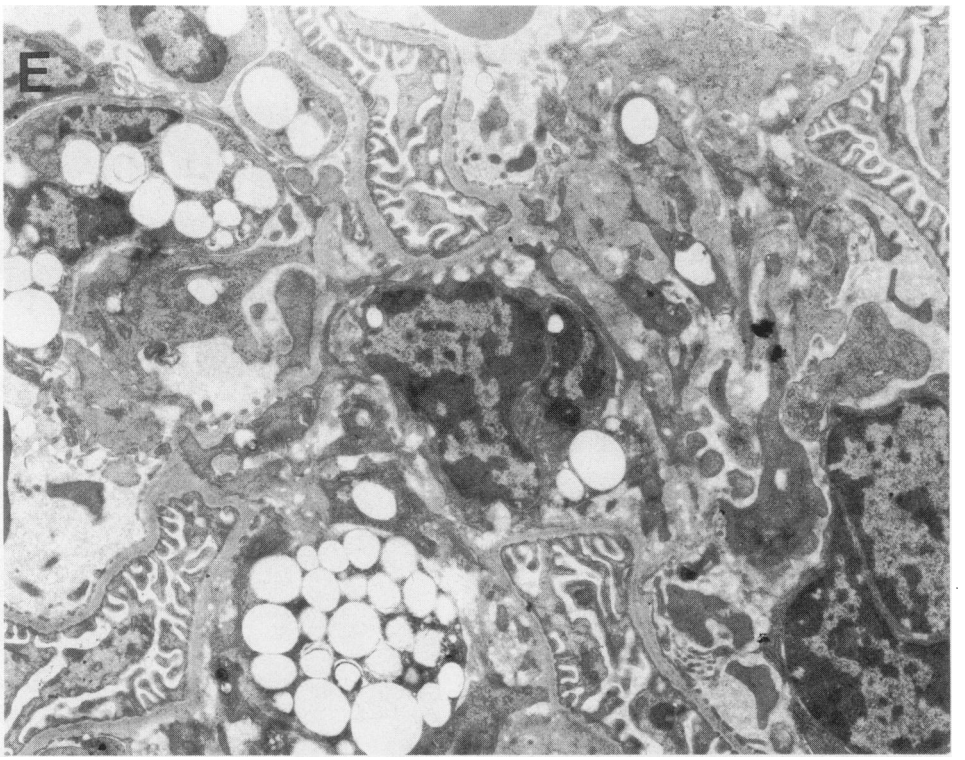
Fig. 5. Kidney of a SZ-treated APA hamster at 3 MAI. Segmental glomerulosclerosis. Foam cells (arrowheads) are seen in mesangial matrix. PAS. ×450.

Fig. 6. Kidney of a control APA hamster at 3 MAI. Slight focal expansion of mesangial region is observed. PAS. ×450.

segmental thickening of basement membrane with increase in electron density, focal effacement of foot processes of podocytes, and swelling and desquamation of a few capillary endothelial cells were observed in some glomeruli. At the same time, lipid-laden mesangial cells and/or foam cells were found in the mesangial matrix and/or beneath the capillary endothelium in a few glomeruli (Fig. 7). Such glomeruli sometimes showed associated lipid embolism (Fig. 8).

Glomerular changes progressed with advancing age and a large portion of some mesangial areas was occupied by foam cells at 3 MAI (Fig. 9). Podocytes frequently showed focal effacement of their foot processes with occasional increase in the amount of electron-dense intracytoplasmic

(7)



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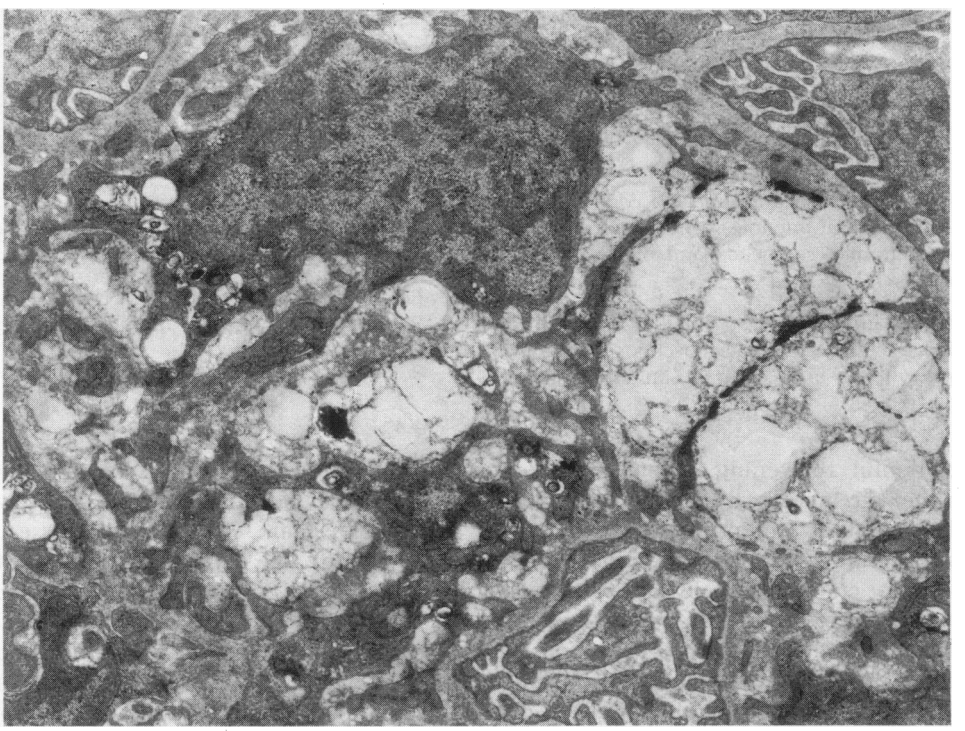

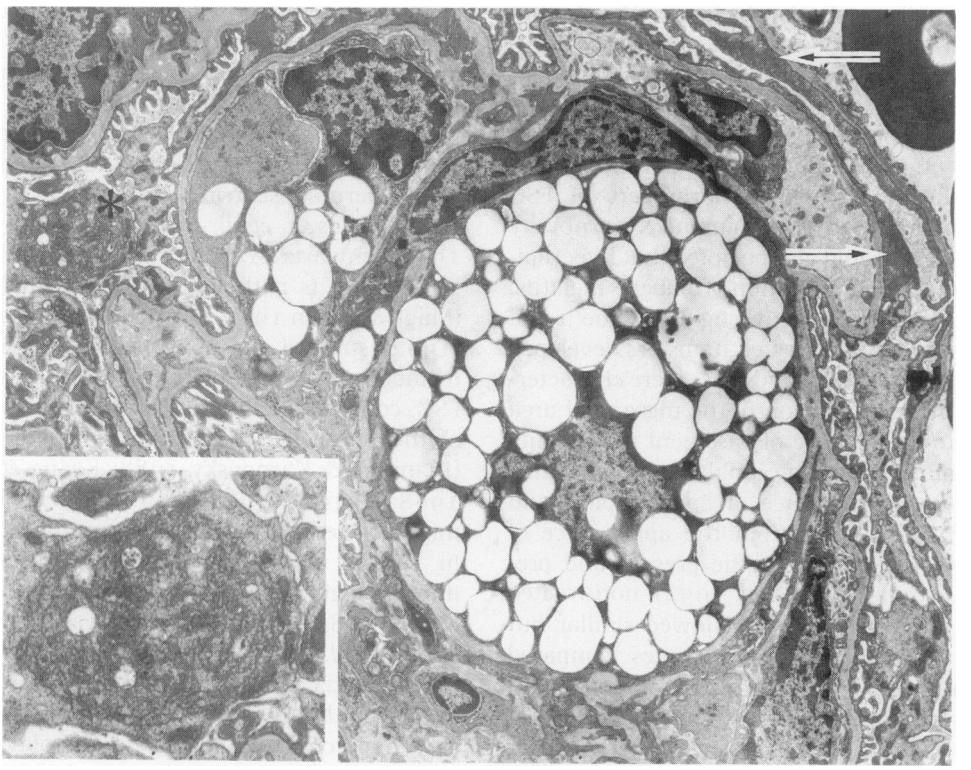

Fig. 9. Glomerulus of a SZ-injected APA hamster at 3 MAI. Foam cell occupies a large portion of mesangial area, and effacement of foot processes of podocytes (arrows) is seen. × 5100. Inset: Larger magnification of a part of podocyte cytoplasm (asterisk). Increase in amount of electron-dense microfilaments is seen. × 12000.

microfilaments, and broad sheets of their cytoplasm were directly applied to the outer surface of capillary basement membranes (Fig. 8). Epithelial cells of Bowman's capsule exhibited swelling and partial destruction and basement membrane of Bowman's capsule showed irregular thickening.

In the glomeruli of control animals, except for the appearance of lipids, similar but less severe changes compared to those in age-matched SZ-injected animals were observed at each time of sacrifice.

Discussion

The serum lipid content of control APA hamsters is thought to be somewhat higher than that of either other Syrian hamsters or other rodents (Han *et al.* 1992; Maxwell *et al.* 1985; Tomson & Wardrop 1987; Wolford *et al.* 1986), and SZ at the dose level of 40 mg/kg induces pronounced, long-lasting hyperglycaemia and hyperlipidaemia with glucosuria in these APA hamsters together with glomerular lipidosis from 1 MAI.

Fig. 7. Glomerulus of a SZ-injected APA hamster at 1 MAI. Lipid-laden mesangial cells and foam cells are seen. E: capillary endothelium. × 6200.

Fig. 8. Glomerulus of a SZ-injected APA hamster at 1 MAI. Lipid embolism is seen in the right half of this figure. × 8300.

Many investigations have shown that hyperlipidaemia is associated with the deposition of lipid macromolecules within glomerular lesions and that mesangial cells might respond by proliferation and production of excess matrix substance, both of which are pathologic harbingers of FSG (Brenner *et al.* 1982; Diamond & Karnovsky 1987). It should also be noted that hyperlipidaemia is a complication of diabetes mellitus.

In the present investigation, the renal glomeruli of SZ-injected hamsters developed segmental lesions, and these were characterized by an expansion of the mesangial area due to an increase of basement membrane-like material and mesangial cells associated with the appearance of lipid droplets and foam cells. Apart from the appearance of lipids, as observed in the present and previous studies (Han *et al.* 1992), non-treated control APA hamsters showed similar but less severe glomerular changes compared with those observed in age-matched SZ-injected APA hamsters. This suggests that the segmental expansion of glomerular mesangial areas was enhanced by glomerular lipidosis in SZ-injected APA hamsters, resulting in formation of FSG.

As to the appearance of lipid embolism in glomerular capillaries of APA hamsters showing marked hyperlipidaemia as well as hyperglycaemia, it is probable that FSG may bring about regional capillary collapse and haemodynamic perturbation (Diamond & Karnovsky 1988), resulting in lipid embolism at that site. Its precise mechanism is however still obscure.

The lesions in SZ-injected APA hamsters were restricted to the juxtamedullary glomeruli at 1 MAI and they extended to the subcapsular glomeruli at 3 MAI. Vulnerability of juxtamedullary glomeruli to FSG is well known (Mizoguchi & Iidaka 1987; Rich 1957), and this is considered to be due to difference in glomerular haemodynamics between juxtamedullary cortex and mid or sub-capsular cortex (Brenner *et al.* 1982; Diamond & Karnovsky 1988; Mizoguchi & Iidaka 1987). In this connection, Rich (1957) stated that glomerular sclerotic lesions in lipoid nephrosis developed in the juxtamedullary region first and then progressed to the subcapsular region.

Currently, FSG is revealed as a pathological diagnosis which describes a distribution of glomerular scarring (Bhathena *et al.* 1980; Goldszer *et al.* 1984; Kiprov *et al.* 1982; Schwartz & Lewis 1985; Zuccheli *et al.* 1983) and its pathogenesis is still unclear (Magil & Cohen 1989). Since Moorhead *et al.* (1982) stressed the abnormalities in lipid metabolism as part of the pathogenesis of FSG, considerable interest has been focused on the role of lipids in the development of FSG (Diamond & Karnovsky 1988; Keane *et al.* 1988; Magil & Cohen 1989). Hyperlipidaemia has been said to be an important factor in several models of experimental non-immunologic glomerular disease (Al-Shebeb *et al.* 1988; Diamond & Karnovsky 1987; Gröne *et al.* 1989; Koletsky 1975; Shimamura 1982), and many researchers have suggested that hyperlipidaemia and alimentary hypercholesterolaemia might play an important role in the progression of FSG. The results of the present investigation support the suggestion that hyperlipidaemia is an important stimulus for the development of FSG in diabetic APA hamsters. In addition, many researchers (Diamond & Karnovsky 1987, 1988; Edwards *et al.* 1977; Grond *et al.* 1986; Keane *et al.* 1988; Kelly & Izui 1983; Moorhead *et al.* 1982; Peric-Golia & Peric-Golia 1983) have suggested that FSG might be analogous to atherosclerosis, and they pointed out many similarities between FSG and atherosclerosis. Foam cells found in atherosclerotic lesions are thought to be derived from both monocyte/macrophage and arterial smooth muscle cells.

The precise cell of origin of glomerular foam cells observed in FSG has been disputed, i.e. endothelial (Hyman & Burkholder 1973; Verani & Hawkins 1986), mesangial (Verani & Hawkins 1986), monocyte/macrophage (Magil & Cohen 1989) and both of monocyte and mesangial cells (Watanabe *et al.* 1982). Foam cells were also observed in the present

study in the affected renal glomeruli of SZ-injected hamsters, and detailed investigation of their origin is now in progress.

In conclusion, SZ-induced diabetic APA hamsters appears to be a useful model for the investigation of glomerular lipidosis and FSG.

Acknowledgements

We thank Drs Katsumi Shimamura, Hiroyuki Akai, and Kazutoshi Tamura, Safety Research Laboratories, Bozo Research Center, for biochemical analysis.

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