Effect of the Lipoprotein Lipase Activator NO-1886 on Adriamycin-Induced Nephrotic Syndrome in Rats

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Hyperlipidemia associated with nephrotic syndrome may play a role in the deterioration of renal function. Tsutsumi et al have previously reported that the novel compound NO-1886 increases lipoprotein lipase (LPL) activity, resulting in a reduction of plasma triglycerides and an elevation of high-density lipoprotein (HDL) cholesterol in normal rats. The aim of this study was to ascertain whether NO-1886 suppresses the renal injury by treatment of the hyperlipidemia in an Adriamycin (Kyowa Hakko Kogyo, Tokyo, Japan) induced nephrosis rat model fed a high-protein diet that induced renal dysfunction and tubulointerstitial injury. Administration of Adriamycin caused hyperlipidemia, proteinuria, and edema with ascites in rats in 4 weeks. Furthermore, a combination of Adriamycin and a high-protein diet increased plasma creatinine and blood urea nitrogen (BUN) and decreased plasma albumin. Histologically, in Adriamycin-treated rats, marked interstitial cellular infiltration, tubular lumen dilation, and tubular cast formation in the kidney were observed. NO-1886 decreased plasma triglyceride and increased HDL cholesterol in Adriamycin-induced nephrotic rats. NO-1886 treatment reduced plasma creatinine and BUN levels and increased plasma albumin in Adriamycin-treated rats; it also ameliorated the ascites and proteinuria. Histologically, NO-1886–treated rats showed a quantitatively significant preservation of tubulointerstitial lesions. These data suggest that NO-1886 may have a protective effect against Adriamycin-induced nephrosis with tubulointerstitial nephritis in rats by a modification of the plasma lipid disorder.

NEPHROTIC SYNDROME is associated with massive proteinuria and hyperlipidemia. When associated with certain types of renal disease such as immunoglobulin A nephropathy, nephrotic syndrome is a factor indicating a poor prognosis.[1-6] Although massive proteinuria is a result of the glomerular injury,[7] the interstitium is also impaired in nephrotic syndrome.[8,9] The histological severity of interstitial injury is more closely related to the decline of renal function.[10-13] In the process of deterioration of renal function, hyperlipidemia is thought to play a significant role. However, the relationship between hyperlipidemia and renal injury has not been elucidated.

The novel compound NO-1886 has been reported to increase lipoprotein lipase (LPL) activity in postheparin plasma and to cause a reduction of plasma triglycerides with a concomitant elevation of high-density lipoprotein (HDL) cholesterol in experimental animals.[14-17] Furthermore, long-term administration of NO-1886 protects against the development of experimental atherosclerosis in rats and rabbits.[14,17]

Few investigations have examined the influence of hyperlipidemia on glomerular and interstitial function in nephrotic syndrome. We investigated the effects of NO-1886 to test whether this LPL activator can improve glomerular and interstitial injury in a rat model that manifests nephrosis and tubulointerstitial injury, as well as renal dysfunction, induced by a combination of Adriamycin treatment and a high-protein diet.

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MATERIALS AND METHODS

Animal Experiments

NO-1886 (4-diethoxyphosphorylmethyl-*N*-(4-bromo-2-cyanophenyl) benzamide) in powder form was obtained from Otsuka Pharmaceutical (Tokushima, Japan). Adriamycin was obtained from Kyowa Hakko Kogyo (Tokyo, Japan). All other chemicals were high-grade commercially available products. Male Sprague-Dawley rats weighing 200 g were purchased from Japan SLC (Shizuoka, Japan). The rats were maintained under a 12-hour light-dark cycle at a constant temperature of 23° ± 2°C.

Preliminary experiments showed that rats injected with Adriamycin (7.5 mg/kg body weight intravenously via a tail vein) develop nephrotic syndrome in 1 week. When the rats were fed with a high-protein diet (including casein equivalent to 40% of total calories) from Oriental Yeast (Tokyo, Japan), all animals developed nephrotic syndrome associated with interstitial injury in 4 weeks. In contrast, rats injected with Adriamycin and fed with a normal diet became nephrotic but did not show interstitial injury or renal dysfunction in 4 weeks. In this experiment, all rats were fed with a high-protein diet. Food consumption was checked daily and body weight was measured weekly.

The rats were divided into 3 groups. Fourteen rats were injected with Adriamycin (7.5 mg/kg body weight) through a tail vein and fed with a high-protein diet (Ad group). Sixteen rats were injected with the same amount of Adriamycin as the Ad group and fed with a high-protein diet containing NO-1886 (Ad + NO group). The amount of food intake was calculated, and the dose of NO-1886 was adjusted to 50 mg/kg/d. The control group (n = 8) was injected with saline and fed with a high-protein diet. Each rat was kept in a metabolic cage for 24 hours and urine samples were collected. All rats were killed at week 4. Before death, the ascites fluid was collected by filter paper and weighed, blood samples were obtained from the abdominal aorta for biochemical analysis, and the kidneys were perfused with 10% buffered Formalin through the abdominal aorta and removed for histological examination.

Biochemical Analysis of Urine and Serum

Twenty-four-hour urinary protein content was measured using the Bio-Rad Protein Assay Kit (Bio-Rad Laboratories, Richmond, CA). Plasma total cholesterol (Cholesterol C-test; Wako Pure Chemical Industries, Osaka, Japan), HDL cholesterol (Nescote HDL-C kit N; Nippon Shoji, Osaka, Japan), and triglyceride (Triglyceride G-test; Wako Pure Chemical Industries) levels were measured using enzymatic methods. Plasma creatinine, blood urea nitrogen (BUN), and albumin were determined by a DRI-CHEM automatic analyzer (Fuji Film, Tokyo, Japan).

Histological Analysis

Kidney specimens were removed after perfusion fixation and further fixed in 10% buffered Formalin and embedded in paraffin. Transverse sections from whole kidney were stained with hematoxylin and eosin, periodic acid-Schiff (PAS), and silver methenamine. Sections were observed with an Olympus BH-2 microscope (Olympus, Tokyo, Japan). Microscopic images of the kidney cortex were captured by a CCD camera (Olympus model CS503MD) and analyzed using a KS400 image-analyzing system (Carl Zeiss Vision Japan, Tokyo, Japan). Some specimens were fixed in 0.2% glutaraldehyde and processed for electron microscopy. Tubulointerstitial pathology was designated as interstitial cellular infiltration, tubular luminal dilatation, and tubular cast formation. The area of interstitial infiltration, tubular dilatation, and cast formation was marked and was quantitatively measured in more than 5 randomly chosen digital photographs made with the CCD camera in microscopic fields (using a 10× objective lens) in each section. The mean area in each rat was calculated, and then the mean area for all rats in each group was calculated and compared.

Statistical Analysis

The results are expressed as the mean ± SD. Comparisons were made by ANOVA followed by Fisher's least-square post hoc test or Student's *t* test or the Aspin-Welch *t* test. Statistical analysis for histological study was performed using a nonparametric Mann-Whitney test.

RESULTS

Food Intake and Body Weight

There were no differences in food intake and body weight between the Ad and Ad + NO groups.

Urinary Protein

Urinary protein excretion was significantly increased in rats injected with Adriamycin. Twenty-four-hour urinary protein excretion 4 weeks after the start of the experiment was 1.14 ± 0.19, 0.96 ± 0.13, and 0.03 ± 0.00 g/d in the Ad group, Ad + NO group, and control group, respectively. There was a statistically significant difference between the Ad and Ad + NO groups ($P < .05$).

Table 2. Correlations for Plasma Lipids and BUN, Creatinine, and Proteinuria in Nephrotic Rats With or Without NO-1886

Lipid	No. of Rats	BUN	Creatinine	Proteinuria
Total cholesterol				
Ad group	14	.584*	−.053	.564*
Ad + NO group	16	.873‡	−.454	.472
HDL cholesterol				
Ad group	14	.422	−.490	.085
Ad + NO group	16	.895‡	−.552*	.438
Triglycerides				
Ad group	14	.670†	−.128	.168
Ad + NO group	16	.781†	−.498*	.391

*$P < .05$.
†$P < .01$.
‡$P < .001$.

Plasma Lipids, BUN, Creatinine, Albumin, and Ascites

Table 1 shows the effects of NO-1886 on plasma lipids, BUN, creatinine, albumin, and ascites. Plasma total cholesterol, HDL cholesterol, triglyceride, BUN, and creatinine levels and ascites were markedly increased in Adriamycin-treated nephrotic rats. Plasma albumin levels were markedly decreased in the nephrotic rat group. Administration of NO-1886 decreased plasma triglycerides ($P < .001$) with a concomitant increase in plasma HDL cholesterol ($P < .001$). The increase in plasma total cholesterol in the Ad + NO group was due to the increase in plasma HDL cholesterol. Furthermore, administration of NO-1886 decreased BUN ($P < .05$), creatinine ($P < .01$), and ascites ($P < .05$) and increased plasma albumin ($P < .05$) in nephrotic rats.

Correlations between plasma lipids and renal function and proteinuria were evaluated. There was a positive correlation between lipids and BUN in the Ad + NO group. There were inverse correlations between HDL cholesterol and triglyceride and creatinine levels in the Ad + NO group (Table 2 and Fig 1).

Histology

Using a light microscope, there were no histological changes in the glomerulus of any of the rats. In the interstitium of rats injected with Adriamycin and fed with a high-protein diet (Ad group), cellular infiltration, mainly mononuclear cells, was found in widespread areas. Dilatation of the tubular lumen was remarkable and observed diffusely in the cortex. Necrotic tubules, atrophic tubules, and tubules containing luminal casts were visible in focal areas (Fig 2). These focal changes were distributed in the whole kidney cortex, but were most severe in

Table 1. Effects of NO-1886 on Plasma Lipids, BUN, Creatinine, Albumin, and Ascites in Adriamycin-Treated Rats

Rat Group	Lipids (mg/dL)			BUN (mg/dL)	Creatinine (mg/dL)	Albumin (g/dL)	Ascites (g)
	Total Cholesterol	HDL Cholesterol	Triglycerides				
Nephrotic							
Ad (n = 14)	460 ± 116	255 ± 90	671 ± 213	128.9 ± 22.4	0.92 ± 0.16	2.09 ± 0.35	12.9 ± 7.4
Ad + NO (n = 16)	711 ± 252†	564 ± 206‡	381 ± 184‡	69.2 ± 29.0*	0.75 ± 0.06†	2.48 ± 0.23*	3.0 ± 2.1*
Control (n = 8)	64 ± 14‡	55 ± 14†	125 ± 45‡	33.3 ± 7.7†	0.54 ± 0.02†	4.03 ± 0.32‡	0.0 ± 0.0‡

NOTE. Data are expressed as the mean ± SD.
*$P < .05$, †$P < .01$, ‡$P < .001$: *v* the respective Ad group.

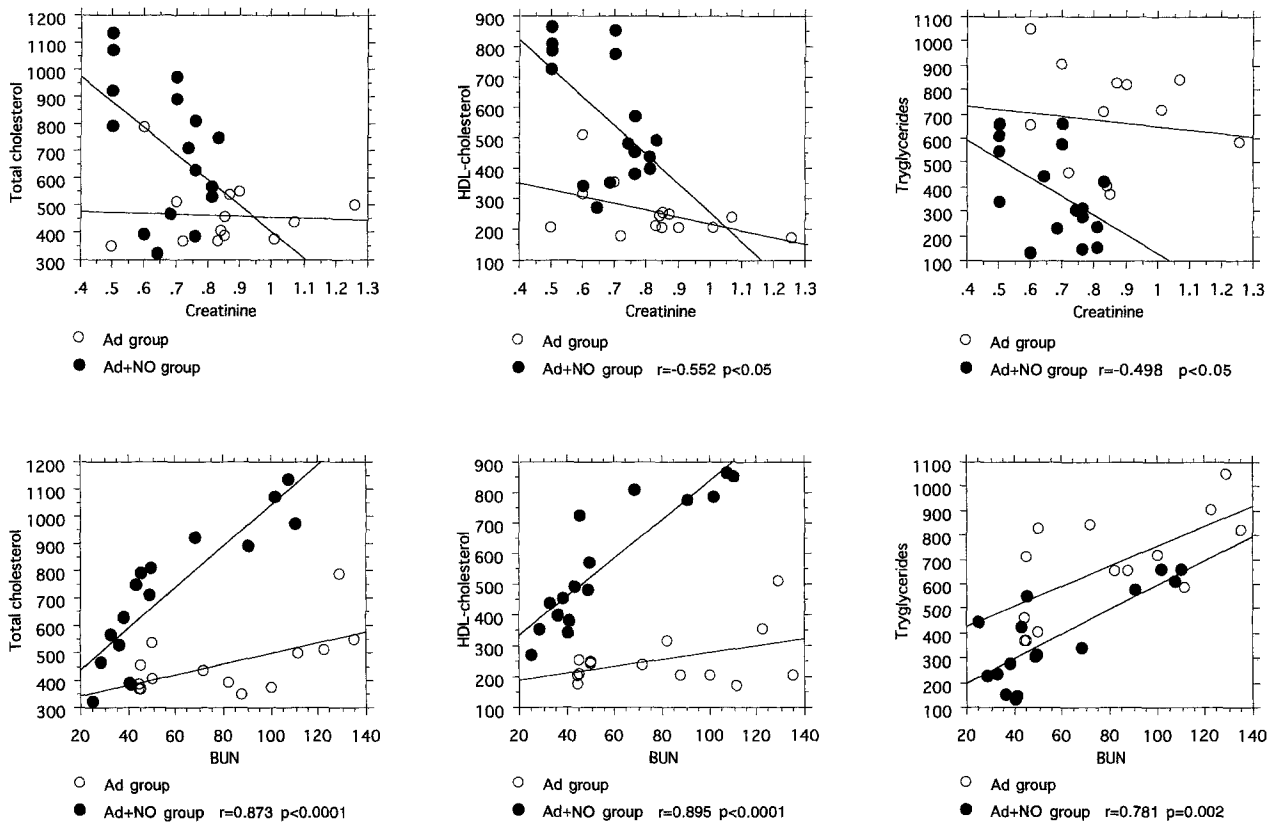

Fig 1. Correlations between plasma lipids and serum creatinine and BUN.

the corticomedullary junction area. Treatment with NO-1886 induced minor interstitial changes, and atrophic or necrotic tubules were not observed (Fig 3). Rats in the control group did not show any interstitial pathological changes (Fig 4). Electron micrographs of the glomerulus from rats in both the Ad and Ad + NO groups showed marked foot-process fusion of glomerular epithelial cells; however, no significant differences were observed.

The mean surface areas of interstitial pathological changes designated as interstitial cellular infiltration, tubular luminal dilatation, and tubular cast formation in each group are listed in Table 3. All pathological abnormalities in the Ad group were marked, and were significantly reduced in the Ad + NO group ($P < .01$ to .05). Rats in the control group did not develop these changes.

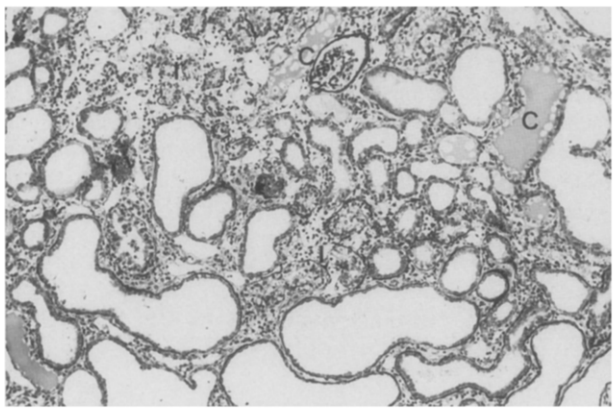

Fig 2. Light microscopic findings of the kidney of a rat in the Ad group. Widespread tubulointerstitial injury is shown. Tubular dilatation with flattened or detached tubular epithelial cells is remarkably visible. Interstitial inflammatory cellular infiltration (I) and tubular casts (c) are also shown. Areas indicated by (I) show the destruction of tubular structure with infiltrated inflammatory cells. PAS stain; original magnification ×200.

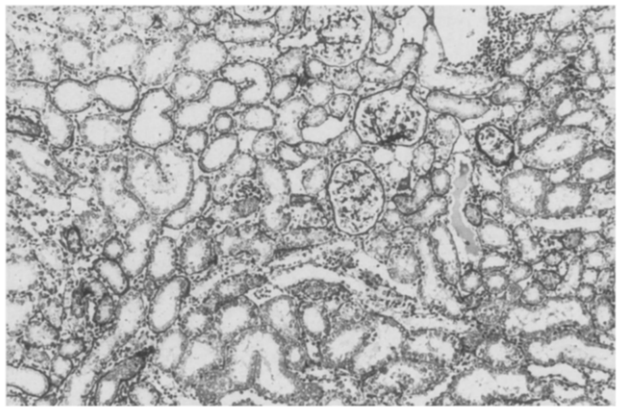

Fig 3. Light microscopic finding of the kidney of a rat in the Ad + NO group. Only a mild degree of interstitial lesion was found compared with nontreated rats. PAS stain; original magnification ×200.

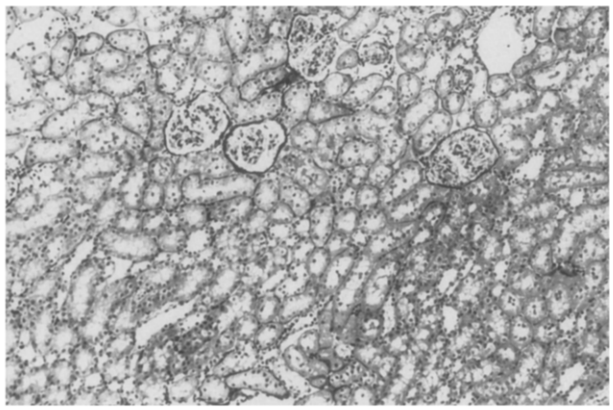

Fig 4. Light microscopic finding of the kidney of a rat in the Control group. No tubulointerstitial lesion is found. PAS stain; original magnification ×200.

DISCUSSION

The Adriamycin-induced nephrosis rat model has been used for the study of the nephrotic syndrome. Although massive proteinuria in the nephrotic syndrome is chiefly a result of glomerular injury, the nephrotic syndrome is often associated with tubulointerstitial injury,[7-9] which is a more important predictor of renal functional loss.[10-13] In this study, we found that when rats were fed with a high-protein diet after injection of Adriamycin, all rats developed interstitial injury in 4 weeks, characterized by inflammatory cellular infiltration, tubular luminal dilatation, and tubular cast formation in addition to massive proteinuria and hyperlipidemia. In contrast, our preliminary study showed that rats injected with Adriamycin and fed with a normal diet developed nephrotic syndrome but did not show tubulointerstitial injury or renal dysfunction. Thus, we decided to use a nephrosis model with a high-protein diet to study the effect of NO-1886 on renal function and tubulointerstitial injury.

NO-1886 is an activator of LPL in plasma and in several organs, resulting in a decrease of triglycerides and an increase of HDL cholesterol.[14-17] Several lipid-lowering agents have been studied in the nephrotic syndrome in humans and animals. In human nephrotic syndrome, lovastatin[18] and simvastatin[19] were effective for improving the hyperlipidemia. Coleman and Watson[20] reported that triglycerides were reduced with simvastatin treatment in pediatric nephrotic syndrome. However, lipid abnormalities differ with the type[21] and stage[22] of the nephrotic syndrome. In rats, a nephrosis model induced with puromycin or Adriamycin has been extensively studied. Lovastatin,[23] 3-thiadicarboxylic acid,[24] alpha tocopherol,[25] and fluvastatin[26] are reportedly effective for improving the lipid metabolism,

Table 3. Mean Surface Area of Interstitial Lesions (% field)

Nephrotic Rats	Tubular Luminal Dilatation	Tubular Cast Formation	Interstitial Cellular Infiltration
Ad group (n = 14)	31.99 ± 10.96	7.22 ± 5.05	3.87 ± 3.18
Ad + NO group (n = 16)	8.52 ± 4.52‡	2.68 ± 2.16†	1.38 ± 0.76*

NOTE. Data are expressed as the mean ± SD.
*$P < .05$, †$P < .01$, ‡$P < .001$: *v* the respective Ad group.

including a decrease of plasma triglycerides and proteinuria. None of these studies reported the effects on tubulointerstitial lesions. In addition, no studies have examined the effect of decreasing triglycerides.

In nephrosis in rats induced by puromycin aminonucleoside or in rats with Heymann nephritis, LPL activity was suppressed in several organs and in the heart at the mRNA level.[27,28] Triglyceride uptake from chylomicrons reduced[29] and triglyceride clearance was decreased,[30,31] whereas triglyceride synthesis was unchanged. Also, very–low-density lipoprotein (VLDL) catabolism was disturbed[32] and VLDL receptor proteins in the heart and muscle were reduced.[33] Hepatic fatty acid–carrier carnitine levels were elevated and hepatic VLDL-bound triglycerides were increased, and thus hepatic triglyceride metabolism was altered.[34]

Our experiment shows that administration of NO-1886 decreased plasma triglycerides and increased HDL cholesterol. Ascites was less prominent, proteinuria was mildly but significantly decreased in treated rats, and renal function was preserved. We could not demonstrate whether these effects of NO-1886 may be due to the LPL effects in this model. NO-1886–treated rats showed a mild improvement in proteinuria. It is not clear whether the difference in proteinuria is due to the direct or indirect effect of NO-1886 on the glomerulus, especially in epithelial cells, which were considered to be affected by puromycin. Morphologically, there was no difference in the glomerulus between NO-1886–treated and untreated rats even at the ultrastructural level. The possibility that a disturbed tubular absorption of albumin resulted in the difference in proteinuria should not be excluded. Ascites formation was significantly prevented in treated rats even though proteinuria was suppressed only mildly. The improvement of hepatic lipid and amino acid metabolism may affect ascites formation.

Hyperlipidemia affects not only the glomerulus but also the interstitium, although the precise mechanism is not known.[8,35-37] It was reported that apolipoprotein B (apo B) is deposited in the interstitium and in tubular cells in nephrotic syndrome.[9] Kasiske et al[37] reported that rats fed with a high-cholesterol diet showed significant tubulointerstitial damage. Oxidized LDL[38,39] and lipid-bound albumin[40,41] are toxic to tubular cells, as well as other factors such as transferrin[42,43] and complement.[44,45] Thomas et al[46] reported that uptake of the fatty acid–albumin complex by a tubular cell line caused accumulation of triglycerides in the cells. These data show that lipid-bound proteins excreted in the urine have further toxic effects on tubular cells in addition to urinary protein itself. The protective effects of NO-1886 on the tubulointerstitial injury in nephrotic rats may be attributable to the improvement of the plasma lipid composition which results in a reduction of lipid-bound urinary protein. It is also possible that NO-1886 acts directly on tubular cells and affects lipid metabolism.

It is well known that HDL cholesterol protects arteries against atherosclerosis, and it was confirmed that NO-1886 protects against atherogenesis in rats[14] and rabbits.[17] However, the effects on the kidneys have not been clarified. In nephrotic syndrome, the level of HDL cholesterol varies. In rat experimental nephrosis, plasma HDL cholesterol is elevated with plasma apo A-1.[47] Apo A-1 mRNA is increased in the liver and

intestine,[48,49] with reduced apo A-1 catabolism in the skin,[50] in nephrotic rats. In our experiment, NO-1886 further increased HDL cholesterol significantly. HDL is easily filtrated in the urine, especially in the nephrotic state, because of its small size. Urinary apo A-1 is increased in Adriamycin-treated nephrotic rats.[50] In our model, the improvement of renal function and proteinuria by NO-1886 treatment may affect the urinary excretion of lipids. A correlation study showed positive correlations between lipids and BUN. In contrast, there were inverse correlations between lipids and creatinine in the Ad + NO group. It is difficult to interpret these results, but it is conceivable that NO-1886 affects creatine metabolism in muscle and modifies the serum creatinine level. The effect of HDL filtration in the urine on tubular epithelial cells could be protective[51] or harmful via the activation of endothelin-1.[52] In addition, modification of HDL in nephrotic plasma might occur.[53] The effect of elevated plasma and urinary HDL is not understood in rat nephrosis.

In conclusion, the novel LPL activator NO-1886 altered the abnormal lipid metabolism in a rat nephrosis model and protected against renal tubulointerstitial injury and renal functional decline.

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