A Novel Peroxisome Proliferator–Activated Receptor (PPAR)γ Agonist, NIP-222, Reduces Urinary Albumin Excretion in Streptozotocin-Diabetic Mice Independent of PPARγ Activation

Takashi Yotsumoto, Takeshi Naitoh, Tatsuro Kanaki, Maho Matsuda, and Nobutomo Tsuruzoe

NIP-222 is a novel peroxisome proliferator–activated receptor (PPAR)γ agonist. This study provides evidence that NIP-222 decreases urinary albumin excretion (UAE) in diabetic mice independent of its PPARγ activation. We compared the effect of NIP-222 and another PPARγ agonist, troglitazone, on UAE, plasma glucose level, blood pressure, and creatinine clearance (C_{cr}) in streptozotocin (STZ)-induced diabetic mice. Treatment for 3 weeks with NIP-222 (30 mg/kg) was associated with a significant decrease in UAE without any change in blood pressure, creatinine clearance, or plasma glucose level. In contrast, UAE did not decrease in mice treated with troglitazone (300 mg/kg). These results indicate that NIP-222 has PPARγ independent effects on UAE in diabetic mice and suggest that this agent may have potential to minimize the development and progression of diabetic nephropathy.

THE SIGNIFICANCE of increased urinary albumin excretion (UAE) as a predictor of diabetic nephropathy in type 1 diabetes is well established. Similarly, in patients with type 2 diabetes, microalbuminuria precedes the onset of overt diabetic nephropathy and is generally regarded as a risk marker for the development of severe renal impairment.[1,2] It is therefore important that patients with microalbuminuria are identified[3] so that appropriate therapy can be started, such as strict glycemic control[4-7] and/or administration of an angiotensin II converting enzyme (ACE) inhibitor.[8] Within the last decade several thiazolidinedione derivatives (TZDs) have been developed for the treatment of type 2 diabetes. TZDs are ligands for nuclear peroxisome proliferator–activated receptor (PPAR)γ and have been shown to improve insulin resistance[9-11] and also decrease albuminuria in patients with early diabetic nephropathy.[12,13] A recent study in streptozotocin (STZ)-induced diabetic rats found that 4 weeks of treatment with the TZD, troglitazone resulted in normalization of glomerular hyperfiltration, although it was not apparent whether this was reflected by a reduction in albuminuria.[14] After 12 weeks of troglitazone, UAE had decreased with this change being independent of hypoglycemia.[14] These results were consistent with an earlier study in the same strain of animals that showed UAE was attenuated within 4 weeks of troglitazone being introduced.[15] In both these studies, troglitazone treatment was started a few days after the injection of streptozotocin to determine the preventive effect of troglitazone on albuminuria.[14,15] There are, however, no reports on the therapeutic effects of PPARγ agonists administered after UAE has developed. The present study addresses this question by investigating the effects of a novel TZD, NIP-222, on increased UAE associated with the diabetic state.

To eliminate the confounding effects on renal function of a reduction in plasma glucose levels after PPARγ activation, we used STZ-induced diabetic mice, a PPARγ agonist-insensitive model. These mice have characteristic features of diabetic nephropathy, such as increased UAE and renal hypertrophy[16] and therefore represent a useful model to evaluate the effects of specific therapies on renal function. To assess the specificity of the renal effects of NIP-222, we compared this agent with troglitazone and also captopril, an ACE inhibitor with proven clinical efficacy in diabetic nephropathy.[17]

MATERIALS AND METHODS

Materials

STZ and captopril were purchased from Sigma (St Louis, MO). The 3 TZDs, 5-[5-{2-hydroxy-2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethoxy}-2-pyridinyl]methyl]-1,3-thiazolidine-2,4-dione (NIP-222), 5-{4-[(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)methoxy]benzyl}-1,3-thiazolidine-2,4-dione (troglitazone), and 5-{4-[2-(methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-thiazolidine-2,4-dione (rosiglitazone) were synthesized at the Chemical Research Laboratories of Nissan Chemical Industries (Funabashi, Japan).

Reporter Plasmids and Luciferase Assays

To generate a fusion protein expression vector (pM- PPARγ) containing residues 204-505 of human PPARγ, the ligand-binding domain (LBD) of human adipose tissue cDNA (Clontech, Palo Alto, CA) was amplified using polymerase chain reaction (PCR) and subcloned into a pM mammalian expression plasmid (Clontech). The reporter plasmid (p4xUASg-tk-luc) contained 4 copies of a 17-bp activating sequence (UAS) upstream of the GAL4 DNA-binding domain and a thymidine kinase gene promoter (tk-promoter) upstream of luciferase cDNA.[18] Cotransfection assays were performed in CV-1 cells using expression vectors for h-PPARγ1-LBD and the p4xUASg-tk-luc reporter.[18] EC_{50} of the test compound was calculated as a concentration and gave 50% of the maximal PPARγ/GAL4 chimera transactivation with 10 μmol/L rosiglitazone, a standard compound of PPARγ activator.

Study on KK-A^y Mice

Male, 8-week-old KK-A^y mice (CLEA Japan, Tokyo, Japan), a murine model of type 2 diabetes, were used as controls in the study. The animals were provided with food and water ad libitum and given oral NIP-222 (30 mg/kg) or troglitazone (300 mg/kg) in a volume of 0.1 mL/10 g body weight. After 24 hours of each compound being administered, a blood sample was collected from the orbital vein plexus using

From the Biological Research Laboratories, Nissan Chemical Industries Ltd, Saitama, Japan.

Submitted March 27, 2003; accepted June 24, 2003.

Address reprint requests to Takashi Yotsumoto, Biological Science Laboratories, Nissan Chemical Industries Ltd, 1470, Shiraoka, Minamisaitama, Saitama 349-0294, Japan.

0026-0495/03/5212-0002$30.00/0
doi:10.1016/j.metabol.2003.06.002

a capillary pipette. Plasma glucose levels were determined with a glucose analyzer II (Beckman, Fullerton, CA).

Study on Mice With STZ-Induced Diabetes

Male, 6-week-old ddY mice (SLC, Shizuoka, Japan) were fasted for 16 hours followed by intraperitioneal injection of a bolus of STZ (150 mg/kg) dissolved in 3 mmol/L citrate buffer (pH 4.5). After 11 days, plasma glucose levels were determined using the glucose analyzer II. Animals with levels >300 mg/dL were selected for the study. On day 12, these diabetic mice were placed in individual metabolism cages for collection of a 24-hour urine sample followed by a blood sample being obtained as described previously. Plasma glucose level was determined with the glucose analyzer and urinary albumin levels determined using a microalbumin-HA test kit (Wako Pure Chemical Industries, Osaka, Japan).

In the first experiment, the STZ-induced diabetic mice were divided into 3 groups to receive 0.5% methyl cellulose (diabetic control, n = 8), 50 mg/kg captopril (n = 10), or 30 mg/kg NIP-222 (n = 10). In a second experiment, STZ-induced diabetic mice were freshly made, and the diabetic mice were divided into 2 groups to receive 0.5% methyl cellulose (diabetic control, n = 9) or 300 mg/kg troglitazone (n = 10). The protocol for both of these experiments was similar and involved daily oral administration of each compound (0.1 mL/10 g body weight) for 3 weeks, starting 14 days after the STZ injection. Food and water were given ad libitum. The mice were placed in individual metabolic cages once a week to collect 24-hour urine samples followed by collection of a blood sample for measurement of plasma glucose level. In the first experiment, systolic blood pressure (SBP) was measured by the tail-cuff method (UR-5000; Ueda, Tokyo, Japan) the day before the mice were placed in the metabolic cages.

At the end of both experiments, the treated mice were killed, and kidney tissues and blood samples were collected. The combined weight of the 2 kidneys (total kidney weight) was determined gravimetrically, with the degree of renal hypertrophy being expressed as the ratio of the total kidney weight to body weight. Renal function was evaluated by measuring creatinine clearance (C_{cr}, mL/min/100 g body weight) with plasma- and urinary-creatinine levels determined using a creatinine test kit (Wako). Urine volume was measured gravimetrically and the urinary albumin level determined as described above.

Statistical Analyses

All results are expressed as the mean ± SEM. Statistical analysis was performed on a Macintosh computer using either Super Anova version 1.11 (Abacus Concepts, Berkeley, CA) or Stat View-J 4.5 (Abacus Concepts). Dunnett's multiple test was used for multiple comparisons, while Student's *t* test was applied for comparisons between 2 groups. Probability values < .05 were considered statistically significant.

RESULTS

Effect of NIP-222 on PPARγ Transactivation in CV1 Cells

Figure 1 shows the effect of NIP-222 on PPARγ transactivation in our luciferase assay system. NIP-222 dose-dependently activated PPARγ/GAL4 chimera transactivation with a 29-fold and 67-fold increase being observed at 0.1 and 1 μmol/L, respectively, compared with control vehicle. Troglitazone also dose-dependently activated PPARγ/GAL4 chimera transactivation with a 13-fold and 46-fold increase at 1 and 10 μmol/L, respectively, compared with control vehicle. The EC_{50} values of NIP-222 and troglitazone were 0.12 μmol/L and 3.41 μmol/L, respectively.

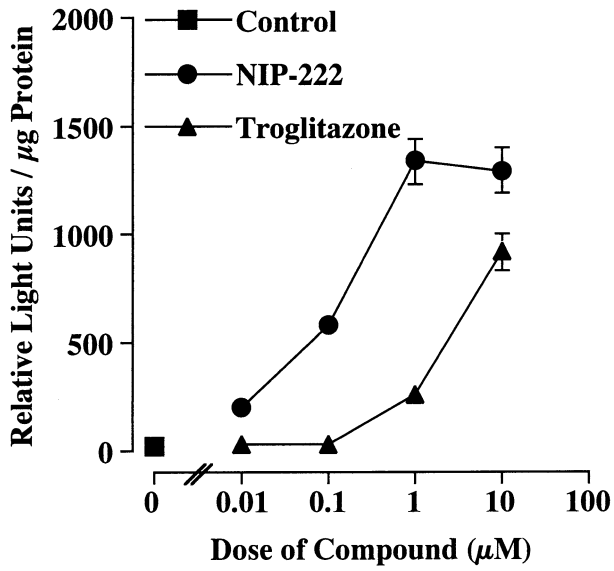

Fig 1. Effects of NIP-222 and troglitazone on PPARγ transactivation in CV1 cells. CV1 cells were cotransfected with p4xUASg-tk-luc (a reporter plasmid regulated by GAL4/PPARγ chimera protein), pM-h PPARγ (an expression plasmid for GAL4/PPARγ chimera protein). Transfected CV1 cells were treated with NIP-222 or troglitazone at various concentrations for 16 hours followed by assay of luciferase activity in the cell extracts. Each value represents the mean ± SEM of 4 replicate tests. EC_{50} of test compound was calculated as a concentration and gave 50% of the maximal PPARγ/GAL4 chimera transactivation with 10 μmol/L rosiglitazone.

Effect of NIP-222 and Troglitazone on Plasma Glucose Levels in KK-A^y Mice

The efficacy of NIP-222 and troglitazone to reduce plasma glucose concentration was investigated in diabetic KK-A^y mice. NIP-222 (30 mg/kg) and troglitazone (300 mg/kg) decreased plasma glucose concentration by 40% (347 ± 15 mg/dL to 206 ± 24 mg/dL; n = 5) and 34% (325 ± 21 mg/dL to 218 ± 44 mg/dL; n = 4), respectively (Fig 2), with the corresponding ED_{25} values of the 2 compounds being 8.9 mg/kg and 161 mg/kg (data not shown).

Effect of Captopril and NIP-222 on Body Weight, Urine Volume, Plasma Glucose, Systolic Blood Pressure, and UAE in STZ-Induced Diabetic Mice

The effect of a 3-week administration of either captopril or NIP-222 on the various parameters is summarized in Table 1. Neither compound had any effect on body weight throughout the experimental period. Urine volume in both diabetic control and captopril-treated mice was increased significantly compared with baseline values, whereas urine volume in the animals receiving NIP-222 did not change. All 3 groups had sustained and marked hyperglycemia (>430 mg/dL), and neither captopril nor NIP-222 significantly altered plasma glucose concentration compared with diabetic controls. Treatment with captopril resulted in a significant decrease in SBP compared with baseline values, while NIP-222 had no effect on SBP.

Captopril treatment significantly reduced UAE by 24% relative to diabetic control. NIP-222 had a similar effect and

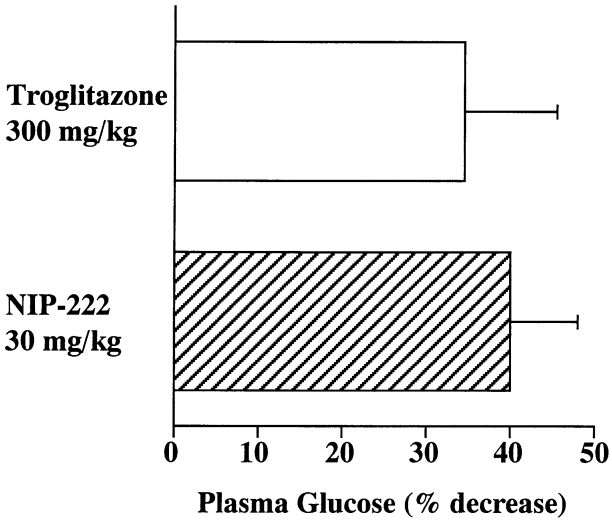

Fig 2. Effects of NIP-222 and troglitazone on plasma glucose level in KK-A^y mice. NIP-222 (30 mg/kg/d, n = 5, hatched-column) and troglitazone (300 mg/kg/d, n = 4, open-column). Values represent mean ± SEM. The blood samples were collected 24 hours after drug administration.

reduced UAE by 28%, in addition to attenuating the time-dependent increment in the level of UAE.

Effect of Troglitazone on Body Weight, Urine Volume, Plasma Glucose, and UAE in STZ-Induced Diabetic Mice

Troglitazone had no effect on body weight throughout the experimental period. There was a trend of increasing urine volume during the study, although this was not statistically significant. Sustained and significant increases in plasma glucose level occurred in both treated and diabetic control animals with levels of greater than 350 mg/dL being maintained throughout the experimental period (Table 2). Troglitazone did not reduce plasma glucose level in these animals.

UAE in the diabetic control group increased significantly by the second week of the experiment (1,411 ± 146 μg/24 hours; data not shown in Table 2) and continued to increase until the end of the study. Three weeks of treatment with troglitazone had no effect on UAE with the level of excretion increasing significantly throughout the study.

Effect of Captopril, NIP-222, and Troglitazone on C_{cr}, Total Kidney Weight, and the Ratio of Total Kidney Weight to Body Weight in STZ-Induced Diabetic Mice

C_{cr} was determined as an index of renal function (Table 3). The diabetic control group in each experiment had a C_{cr} level of 1.33 ± 0.07 and 1.17 ± 0.14 mL/min/100 g body weight. These values are approximately 3-fold higher than in nondiabetic mice we reported previously (0.40 ± 0.05 mL/min/100 g body weight (n = 10).[16] Neither captopril, NIP-222, nor troglitazone altered C_{cr}.

Renal hypertrophy was assessed by calculating the ratio of kidney weight to body weight in the various groups of mice. We have shown previously [16] that both kidney weight and ratio increased 49 days after injection of STZ (0.567 ± 0.025 g and 0.189 ± 0.008, respectively). However, the kidney weight increase was not significantly different from the increment seen in age-matched nondiabetic mice (0.497 ± 0.025 g and 0.133 ± 0.005). In the present study, the diabetic control animals had a total kidney weight of 0.515 ± 0.015 g and 0.525 ± 0.031 g with the ratio of total kidney weight to body weight being 0.164 ± 0.004 and 0.169 ± 0.011, respectively. Neither parameter was altered by 3 weeks of treatment with captopril, NIP-222, or troglitazone.

DISCUSSION

The early stages of diabetic nephropathy are characterized by an elevation in UAE, increased glomerular filtration rate (GFR), and renal hypertrophy.[19,20] In this study, we demonstrated clearly that a novel PPARγ agonist, NIP-222, reduced UAE in STZ-induced diabetic mice without affecting either blood glucose level or glomerular function assessed by C_{cr}. In contrast, a different PPARγ agonist, troglitazone, had no effect on UAE in STZ-induced diabetic mice, although the effect of troglitazone (300 mg/kg) on hypoglycemic activity was similar to that of NIP-222 (30 mg/kg) in KK-A^y mice (Fig 2). We adopted these doses because we decided that the results in vivo were more practical than those in vitro, although the results of PPARγ transactivation in vitro (Fig 1) showed that the EC_{50} of NIP-222 was 28-fold smaller than that of troglitazone. Our data suggests that the mechanism of the reduction in UAE associated with NIP-222 is also different from that of captopril, as it appeared not to be related to decreases in SBP. Taken together, our results suggest that the effect of NIP-222 on UAE are not

Table 1. Effects of 3 Weeks of Treatment With Either Captopril or NIP-222 on Body Weight, Urine Volume, Plasma Glucose, Systolic Blood Pressure, and Urinary Albumin Excretion in STZ-Treated Mice

Parameters	Group	Pretreatment	Week 3
Body weight (g)	Diabetic control	30.2 ± 0.6	31.4 ± 0.6
	Captopril	32.4 ± 0.9	32.9 ± 0.8
	NIP-222	32.6 ± 0.9	32.5 ± 1.7
Urine volume (g)	Diabetic control	18.9 ± 3.4	31.2 ± 2.5†
	Captopril	20.3 ± 3.6	29.6 ± 3.6†
	NIP-222	22.4 ± 3.2	21.1 ± 3.9
Plasma glucose (mg/dL)	Diabetic control	438 ± 16	474 ± 6
	Captopril	443 ± 20	460 ± 25
	NIP-222	440 ± 21	523 ± 46
Systolic blood pressure (mm Hg)	Diabetic control	142.5 ± 4.9	145.0 ± 3.4
	Captopril	140.0 ± 4.8	127.7 ± 4.8†
	NIP-222	141.1 ± 4.5	153.3 ± 8.7
Urinary albumin excretion (μg/24 h)	Diabetic control	1,075 ± 68	1,483 ± 164†
	Captopril	1,096 ± 71	1,125 ± 97*†
	NIP-222	1,122 ± 70	1,071 ± 92*

NOTE. Values represent mean ± SEM. Diabetic control (n = 8); captopril (50 mg/kg/d, n = 10); NIP-222 (30 mg/kg/d, n = 10). Test compounds were administered orally 14 days after STZ injection. The pretreatment value indicates urinary albumin excretion 12 days after STZ injection.

*$P < .05$, significantly different from controls (Dunnett's multiple test).

†$P < .05$, significant difference from pretreatment (paired t test).

Table 2. Effects of Troglitazone Given for 3 Weeks on Body Weight, Urine Volume, Plasma Glucose, and Urinary Albumin Excretion in STZ-Treated Mice

Parameters	Group	Pretreatment	Week 3
Body weight (g)	Diabetic control	32.0 ± 1.2	31.1 ± 1.0
	Troglitazone	31.0 ± 1.6	32.5 ± 1.8
Urine volume (g)	Diabetic control	23.0 ± 3.5	23.4 ± 5.1
	Troglitazone	25.0 ± 3.4	31.0 ± 3.7
Plasma glucose (mg/dL)	Diabetic control	362 ± 15	466 ± 36*
	Troglitazone	350 ± 15	497 ± 18*
Urinary albumin excretion (μg/24 h)	Diabetic control	1,109 ± 53	1,275 ± 171
	Troglitazone	1,135 ± 57	1,486 ± 125*

NOTE. Values represent mean ± SEM. Diabetic control (n = 9) and troglitazone (300 mg/kg/d, n = 10), started 14 days after STZ injection. The pretreatment value indicates urinary albumin excretion 12 days after STZ injection. Comparison of the 2 groups using Student's *t* test showed no significant difference.

*$P < .05$, significantly different from pretreatment value (paired *t* test).

dependent on PPARγ activation, hypoglycemic activity, decreasing SBP, or changes in renal hemodynamics.

Our findings are consistent with 2 earlier studies in STZ-induced diabetic rats that found troglitazone prevented increases in UAE regardless of changes in blood glucose levels.[14,15] The more recent of these studies demonstrated 12 weeks of treatment with either troglitazone or pioglitazone in diabetic rats inhibited activation of the diacylglycerol (DAG)-protein kinase C (PKC) extracellular signal-regulated kinase (ERK) pathway in both glomeruli and mesangial cells cultured in vitro under hyperglycemic conditions.[14] These findings lead to speculation that the development of glomerular dysfunction in STZ rats could be prevented by inhibiting the DAG-PKC-ERK pathway, and that this action may have been mediated by the thiazolidinedione moiety in both compounds. In our study, NIP-222, but not troglitazone treatment, reduced UAE once overt proteinuria had become established. It appears likely that this effect of NIP-222 is not mediated by the thiazolidinedione structure. This result suggests strongly that the effect of NIP-222 and troglitazone have different effects on glomerular function and protein ultrafiltration, although the role of the thiazolidinedione moiety in the reduction in UAE remains unclear.

These earlier studies also observed decreased UAE[15] and GFR and filtration fraction fell to within the normal range[14] within 4 weeks of treatment with troglitazone. Unfortunately, this latter study did not measure whether normalization of hyperfiltration was associated with a decline in UAE. In our study, troglitazone had no effect on the high UAE levels in the diabetic mice. This finding may have differed from the results of the earlier studies as a consequence of the stage in the disease process at which treatment was introduced. In our study, troglitazone treatment was started 14 days after the STZ injection by which time overt proteinuria was present, whereas in these other studies, treatment was started before any significant increase in UAE had occurred, ie, the second day in Isshiki et al[14]) and the seventh day in Fujii et al.[15]

The effect of delayed ACE inhibition in our study on the progression and reversal of established nephropathy is also not clear, although it is generally accepted that early treatment seems to be more renoprotective.[21-24] The small number of studies that have investigated early versus late ACE intervention found only early treatment normalized glomerulosclerosis and albuminuria in rats with mild diabetic nephropathy.[25,26]

PPARγ is expressed in the glomerular fraction of rat kidney, localized in the nuclei of mesangial cells, and have the potential to activate a PPARγ response element (PPRE).[27] The PPARγ ligands, troglitazone and 15-deoxy-$\Delta^{12,14}$-prostaglandin J2, significantly suppress the production of α-smooth muscle actin, indicating that PPARγ activation may inhibit dedifferentiation of mesangial cells.[28] As PPARγ ligands inhibit proliferation of mesangial cells in a dose-dependent manner,[28] PPARγ activation has the ability to reverse the phenotypic change of mesangial cells, retard cell growth, and reduce extracellular matrix production, thereby preventing diabetic-induced renal hypertrophy. The finding that 12 weeks of treatment with troglitazone was required to significantly decrease kidney mass in diabetic rats with this effect not being apparent at 4 weeks is consistent with such a mechanism.[14] We have demonstrated previously[16] that UAE in diabetic mice was attenuated after only 5 weeks of treatment with captopril, an agent with proven

Table 3. Effects of Captopril, NIP-222, and Troglitazone on Creatinine Clearance and Renal Hypertrophy in STZ-Treated Mice

Group	Dose (mg/kg/d)	No.	Ccr (mL/min/100 g body weight)	Total Kidney Weight (g)	Kidney Weight/10 g Body Weight
Diabetic control		8	1.33 ± 0.07	0.515 ± 0.015	0.164 ± 0.004
Captopril	50	10	1.55 ± 0.26	0.510 ± 0.026	0.155 ± 0.021
NIP-222	30	10	1.78 ± 0.22	0.540 ± 0.031	0.168 ± 0.009
Diabetic control		9	1.17 ± 0.14	0.525 ± 0.031	0.169 ± 0.011
Troglitazone	300	10	1.27 ± 0.12	0.523 ± 0.035	0.161 ± 0.006

NOTE. Values represent mean ± SEM. Test compounds were given orally daily 14 days after STZ injection. Comparison of the groups using Student's *t* test and Dunnett's multiple test showed no significant differences.

clinical efficacy in diabetic nephropathy.[17,29] However, in the present study, captopril while decreasing kidney mass had no marked effect on renal hypertrophy, possibly as a consequence of the experimental period being too short for the development of diabetic renal hypertrophy.

In conclusion, the novel PPARγ agonist, NIP-222, administered for 3 weeks to STZ-induced diabetic mice attenuated the increase in UAE independent of hypoglycemic activity, decreased systolic blood pressure, or changes in renal hemodynamics. In contrast, troglitazone introduced 14 days after the initiation of diabetes had no effect on high UAE. These results suggest NIP-222 has a more potent and rapid antialbuminuric action than troglitazone, and that the effects were independent of the PPARγ activation and/or the thiazolidinedione moiety in the compound. NIP-222 may have potential for minimizing the development and progression of diabetic nephropathy.

REFERENCES

1. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 310:356-360, 1984
2. Alzaid AA: Microalbuminuria in patients with NIDDM: An overview. Diabetes Care 19:79-89, 1996
3. Mogensen CE, Keane WF, Bennet PH, et al: Prevention of diabetic renal disease with special reference to microalbuminuria. Lancet 346:1080-1084, 1995
4. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329:977-986, 1993
5. Ohkubo Y, Kishikawa H, Araki E, et al: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomized prospective 6-year study. Diabetes Res Clin Prac 28:103-117, 1995
6. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837-853, 1998
7. UK Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352:854-865, 1998
8. Marre M, Leblanc H, Suarez L, et al: Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria. Br Med J 294:1448-1452, 1987
9. Henry RR: Thiazolidinediones. Endocrinol Metab Clin North Am 26:553-573, 1997
10. Saku K, Zhang B, Ohta T, et al: Troglitazone lowers blood pressure and enhances insulin sensitivity in Watanabe heritable hyperlipidemic rabbits. Am J Hypertens 10:1027-1033, 1997
11. Walker AB, Chattington PD, Buckingham RE, et al: The thiazolidinedione rosiglitazone (BRL-49653) lowers blood pressure and protects against impairment of endothelial function in Zucker fatty rats. Diabetes 48:1448-1453, 1999
12. Imano E, Kanda T, Nakatani Y, et al: Effect of troglitazone on microalbuminuria in patients with incipient diabetic nephropathy. Diabetes Care 21:2135-2139, 1998
13. Nakamura T, Ushiyama C, Shimada N, et al: Comparative effects of pioglitazone, glibenclamide, and voglibose on urinary endothelin-1 and albumin excretion in diabetes patients. J Diabetes Complications 14:250-254, 2000
14. Isshiki K, Haneda M, Koya D, et al: Thiazolidinedione compounds ameliorate glomerular dysfunction independent of their insulin-sensitizing action in diabetic rats. Diabetes 49:1022-1032, 2000
15. Fujii M, Takemura R, Yamaguchi M, et al: Troglitazone (CS-045) ameliorates albuminuria in streptozotocin-induced diabetic rats. Metabolism 46:981-983, 1997
16. Yotsumoto T, Naitoh T, Shikada K, et al: Effects of specific antagonists of angiotensin II receptors and captopril on diabetic nephropathy in mice. Jpn J Pharmacol 75:59-64, 1997
17. Foote EF: Prevention and treatment of diabetic nephropathy. Am J Health Syst Pharm 52:1781-1792, 1995
18. Takahashi N, Kawada T, Goto T, et al: Dual action of isoprenols from herbal medicines on both PPARγ and PPARα in 3T3-L1 adipocytes and HepG2 hepatocytes. FEBS Lett 514:315-322, 2002
19. Mogensen CE, Christensen CK: Predicting diabetic nephropathy in insulin-dependent patient. N Engl J Med 311:89-93, 1984
20. Mogensen CE, Andersen MJF: Increased kidney size and glomerular filtration rate in untreated juvenile diabetes: Normalization by insulin-treatment. Diabetologia 11:221-224, 1975
21. Allen TJ, Cao Z, Youssef S, et al: The role of angiotensin II and bradykinin in experimental diabetes nephropathy: Functional and structural studies. Diabetes 46:1612-1618, 1997
22. Anderson S, Rennke HG, Garcia DL, et al: Short and long term effects of antihypertensive therapy in the diabetic rat. Kidney Int 36:526-536, 1989
23. Geiger H, Fierlbeck W, Mai M, et al: Effects of early and late antihypertensive treatment on extracellular matrix proteins and mononuclear cells in uninephrectomized SHR. Kidney Int 51:750-761, 1997
24. Verseput GH, Koomans HA, Braam B, et al: ACE inhibition delays development of terminal renal failure in the presence of severe albuminuria. Am J Kidney Dis 35:202-210, 2000
25. Perico N, Amuchastegui SC, Colosio V, et al: Evidence that an angiotensin-converting enzyme inhibitor has a different effect on glomerular injury according to the different phase of the disease at which the treatment is started. J Am Soc Nephrol 5:1139-1146, 1994
26. Cooper ME, Allen TJ, MacMillan P, et al: Genetic hypertension accelerates nephropathy in the streptozotocin diabetic rat. Am J Hypertens 1:5-10, 1988
27. Nicholas SB, Kawano Y, Wakino S, et al: Expression and function of peroxisome proliferator-activated receptor-γ in mesangial cells. Hypertension 37:722-727, 2001
28. Asano T, Wakisaka M, Yoshinari M, et al: Peroxisome proliferator-activated receptor gamma1 (PPARgamma1) expresses in rat mesangial cells and PPARgamma agonists modulate its differentiation. Biochim Biophys Acta 1497:148-154, 2000
29. Björck S, Mulec H, Johnsen SA, et al: Renal protective effect of enalapril in diabetic nephropathy. Br Med J 304:339-343, 1992