

Original Article

Protective Effect of *Stachybotrys microspora* Triprenyl Phenol-7 on the Deposition of IgA to the Glomerular Mesangium in Nivalenol-induced IgA Nephropathy Using BALB/c Mice

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Abstract: Activators of tissue proteolysis including *Stachybotrys microspora* triprenyl phenol (SMTP)-7 are a new class of agents that are expected to be effective for amelioration of chronic tissue destructive diseases. The present study was performed to examine whether SMTP-7 is effective for the amelioration or protection of early-stage IgA nephropathy (IgAN) induced by nivalenol (NIV) in female BALB/c mice. In Experiment 1, mice were administered NIV at 24 ppm in diet for 8 weeks, and during the NIV treatment, they were intraperitoneally injected with SMTP-7 (10 mg/kg) three times a week. In Experiment 2, mice were injected similarly with SMTP-7 during the last 4 weeks of a 16-week NIV treatment. Immunofluorescence analysis revealed an inhibitory effect of SMTP-7 on the glomerular deposition of IgA in Experiment 1; however, it was ineffective in Experiment 2. On the other hand, SMTP-7 did not affect the serum concentration of IgA in both experiments. These results suggest that SMTP-7 has a potential to decrease the progression of IgAN induced by NIV through inhibition of local accumulation of IgA in the glomerular mesangium, while it was ineffective for suppression of IgA production. On the other hand, SMTP-7 was found to be ineffective for already deposited IgA, suggesting that SMTP-7 may not be effective for ameliorating advanced IgAN. (DOI: 10.1293/tox.25.149; J Toxicol Pathol 2012; 25: 149–154)

Key words: *Stachybotrys microspora* triprenyl phenol-7, IgA nephropathy, BALB/c mice, nivalenol

Introduction

Stachybotrys microspora triprenyl phenols (SMTPs), a family of triprenyl phenol metabolites of *Stachybotrys microspora*, enhance fibrinolysis by modulating plasminogen conformation to increase its susceptibility to activation by plasminogen activators¹. The plasminogen/plasmin system is involved in a variety of physiological and pathological processes requiring localized proteolysis, such as fibrinolysis, inflammation, tissue remodeling, ovulation, tumor metastasis and tissue invasion of pathogens^{2–6}. SMTP-7 is an isotype of SMTPs (SMTP 1–8), and its molecule consists of

two identical staplabin core structures and ornithine, which bridges the two partial structures (Fig. 1). Cell-free study has shown that SMTP-7 enhances by several fold urokinase-catalyzed plasminogen activation and plasminogen-fibrin binding as well as urokinase- and plasminogen-mediated fibrinolysis at concentrations of 80–150 μM ⁷. SMTP-7 has been shown to provide useful tools for studies of the conformational regulation of plasminogen activation as well as for the development of antithrombotic agents⁷. Recent studies have shown the *in vivo* efficacy of SMTP-7 for suppression of inflammation, superoxide production and matrix metalloproteinase-9 expression in rodent brain ischemia models^{8,9}, suggesting its effectiveness in the suppression of chronic disease requiring tissue remodeling.

Human IgA nephropathy (IgAN) is the most common primary chronic glomerulonephritis in Japan, and approximately 40–50% of all cases cause end-stage renal dysfunction after a course of no less than 20 years¹⁰. IgAN is the most common primary chronic nephropathy, and histopathological changes characterized by expansion of glomerular mesangial matrix and mesangial proliferation develop after the long period of the disease process¹¹, which is suggestive

Received: 7 December 2011, Accepted: 18 January 2012

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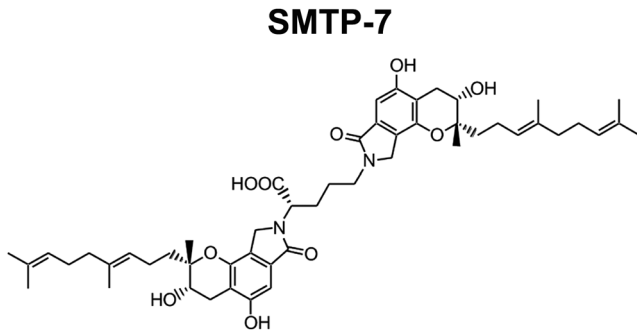


Fig. 1. Structural formula of SMTP-7 (molecular weight, 869.1; CAS no. 273379-50-9).

of progressive glomerular remodeling. However, the precise mechanisms are not fully understood. In experimental animals, dietary administration of nivalenol (NIV) or deoxynivalenol (DON), trichothecene mycotoxins produced by *Fusarium* fungi, to mice results in an elevation of serum IgA levels and its deposition in the glomerular mesangium^{12,13}, resembling IgAN in humans. Our previous study suggested that BALB/c mice fed a basal diet at a concentration of 12 or 24 ppm showed a dose-dependent elevation in the serum concentration of IgA and its deposition in the glomerular mesangium, which is suggestive of development of early IgAN¹⁴.

It is now important to accumulate knowledge concerning whether SMTP-7 has a therapeutic potential against disease conditions requiring tissue remodeling. Actually, a series of *in vivo* studies have recently been reported regarding the effectiveness of SMTP-7 in ameliorating brain ischemia/reperfusion injury in rats or mice^{8,9,15–17}. The present study was aimed at elucidating whether SMTP-7 has a therapeutic potential against IgAN, and we examined its effectiveness in regard to amelioration or protection during the early process of IgAN induced by NIV in BALB/c mice.

Materials and Methods

Chemicals

The nivalenol (NIV) used in this study was purified in the Division of Microbiology, National Institute of Health Sciences, Japan. For purification of NIV, Fusarenon X was extracted and purified from culture media of *Fusarium kyushuense* (Fn-2B). The identity and purity of NIV were determined by liquid chromatography/mass spectrometry (LC/MS; LCMS-2010A, Shimadzu Corp., Kyoto, Japan) with an atmospheric pressure chemical ionization interface and an LC system (LC-2010CHT, Shimadzu Corp.), and the purity was estimated to be >98% from the area percentage of the chromatogram^{18,19}. For administration to mice, NIV was first dissolved in a small quantity of ethanol and then well mixed into powdered MF basal diet (Oriental Yeast Co., Ltd., Tokyo, Japan). Stability of the test compound in the diet was confirmed for up to 2 weeks at room temperature (> 92%). Therefore, test diets were prepared every 2 weeks and stored at 4°C before use^{18,19}.

Production of SMTP-7

A loopful of a slant culture of *Stachybotrys microspora* IFO 30018 was inoculated into a 500-ml Erlenmeyer flask containing 100 ml of medium consisting of 3% glucose, 1% soybean meal, 0.3% peptone, 0.3% meat extract, 0.3% yeast extract, 0.05% KH₂PO₄, 0.05% MgSO₄·7H₂O and 0.01% CB442 (an antifoam agent, Nippon Oil & Fats Co., Ltd., Tokyo, Japan). The flask was incubated at 25°C for 3 days on a rotary shaker at 180 rpm. A 1-ml portion of the seed culture was inoculated into a 500-ml Erlenmeyer flask containing 100 ml of medium consisting of 2% glucose, 0.5% peptone, 0.3% yeast extract, 0.3% KH₂PO₄, 0.1% MgSO₄·7H₂O and 0.01% CB442 (pH 5.5), and the flask was incubated as above for 11 days⁷.

Isolation of SMTP-7

SMTP-7 was produced as minor metabolites along with staplabin and SMTP-4, 5 and 6. The combined culture supernatant (9.15 liters) was extracted with 2-butanone (once with 9 liters and twice with 4.5 liters). The organic layer was concentrated, giving 3.89 g of an oily residue. The residue was applied to a silica gel column (30 × 240 mm), and the column was eluted successively with a mixture of dichloromethane and methanol (98:2, 95:5, 90:10 and then 80:20; 3.9 liters each). SMTP-7 was found in the 80:20 fraction, which was concentrated to give 143 mg of a residue. This material was subjected to preparative HPLC on an Inertsil PREP-ODS column (30 × 250 mm; GL Sciences, Tokyo, Japan), which was developed at 40°C with 50 mM ammonium acetate in 80% aqueous methanol at a rate of 25 ml/minute. The fraction containing SMTP-7 (retention time, 22.0–24.5 minutes) was evaporated to remove methanol and extracted with ethyl acetate, giving 8.0 mg of purified SMTP-7⁷.

Animals and experimental design

Animal studies consisted of two experiments analyzing the effect of SMTP-7 on early-stage IgA deposition in the glomerular mesangium (Experiment 1) and on already deposited IgA (Experiment 2). Female BALB/c Cr Slc mice were purchased from Japan Slc, Inc. (Shizuoka, Japan) at 5 weeks of age, received powdered diets and tap water *ad libitum* during the acclimation week and were kept in polycarbonate cages with white wood chips for bedding in an air-conditioned animal room (24 ± 1°C, 55 ± 5% relative humidity, 12 h light and dark cycle).

In Experiment 1, animals were divided into three groups consisting of 12 (NIV-alone), 14 (NIV+SMTP-7) and 8 (untreated controls). Animals in the NIV-alone and NIV+SMTP-7 groups were fed a diet containing 24 ppm NIV for 8 weeks. Animals in NIV+SMTP-7 group underwent intraperitoneal injections of SMTP-7 (10 mg/kg) dissolved in saline at three times a week for 8 weeks.

In Experiment 2, animals were divided into three groups consisting of 12 (NIV-alone), 14 (NIV+SMTP-7) and 8 (untreated controls) as in Experiment 1. Animals in the NIV-alone and NIV+SMTP-7 groups were fed a diet containing 24 ppm NIV for 16 weeks. Mice in the NIV+SMTP-7

group were injected with SMTP-7 in the same way as in Experiment 1, but only for the last 4 weeks of the 16-week NIV treatment.

The dosage (24 ppm) and periods (8 or 16 weeks) of the NIV treatments were based on our previous study¹⁴. Body weight, food intake and water consumption were measured once a week. After 8 weeks (Experiment 1) or 16 weeks (Experiment 2) of NIV treatment, all animals were anesthetized with ether, and blood samples were collected from the abdominal aorta for measurement of serum IgA and IgG concentrations at Mitsubishi Chemical Medience (Tokyo, Japan). The animals were then euthanized by exsanguination from the posterior vena cava and abdominal aorta. Kidneys were collected from all animals, weighed and fixed in phosphate-buffered 10% formalin, pH 7.4, or frozen in liquid nitrogen immediately after embedding in Tissue-Tek 4583 OCT Compound (Sakura Finetek Japan, Tokyo, Japan) and stored at -80°C .

Animal care and experiments were carried out in accordance with the guidelines for animal experimentation of the Facility of Agriculture, Tokyo University of Agriculture and Technology.

Histopathology and immunofluorescence

Formalin-fixed kidney tissues were embedded in paraffin, and tissue slices were sectioned for histopathological examinations after staining with hematoxylin and eosin. For immunofluorescence analysis, frozen tissues were sectioned at a thickness of 4 μm and fixed with cold acetone at -20°C for 5 minutes. Using an indirect immunofluorescence method for the detection of IgA, goat anti-mouse IgA (Kirkegaard & Perry Laboratories, Gaithersburg, MD, USA) antibody was applied at a dilution of 1:1000 followed by incubation with fluorescein isothiocyanate conjugated anti-goat immunoglobulins (Dako, Glostrup, Denmark) at a dilution of 1:100. The fluorescence was detected with a confocal laser scanning microscope (Leica TCS NT, Leica Microsystems, Heidelberg, Germany). FITC was excited at 488 nm using an argon/krypton laser, and the fluorescence was selected by a 530 nm band-pass filter. The emitted fluorescence signals were visualized by calculation of the average pixel value of 4 frame scans. For evaluation of the immunoreactivity of IgA in glomeruli, the intensity of fluorescence staining was visually scored as 0 (none), 1 (slight), 2 (moderate) or 3 (strong) by observation of five randomly selected areas including approximately 12–15 glomeruli/mice at a 200-fold magnification. Assessment of the quantitative intensity value was performed using the WinROOF image analysis software package (version 5.7, Mitani Corporation, Fukui, Japan). To assess the IgA precipitation in the glomerulus, the background intensity surrounding the glomerulus was subtracted from the raw intensity in the glomerulus.

Statistics

Numerical data including body weight and water consumption during experiments, serum IgA levels, kidney weights (both absolute and relative weights) and quantitative

analysis of immunoreactivity of IgA in glomeruli was checked for homogeneity of variance using Bartlett's test. If the variance was homogeneous, the data were assessed by Tukey's multiple test of variance. If not, the Steel-Dwass multiple test was applied. Comparison was first made between the untreated controls and NIV-treated groups and then between the NIV-alone group and NIV+SMTP-7 group. Scores for immunostaining intensity of IgA in glomeruli were compared between the untreated controls and NIV-treated groups and between the NIV-alone group and NIV+SMTP-7 group using the Mann-Whitney U test. A P value of less than 0.05 was considered statistically significant.

Results

Body and kidney weights

In Experiment 1, one animal in the NIV-alone group that exhibited weight loss during the animal study died. No significant changes were observed in food intake and water consumption between the untreated controls and NIV-treated groups and also between the NIV-alone and NIV+SMTP-7 groups (data not shown). From week 3 of treatment with NIV through to necropsy, we observed a significant decrease in the body weight of both NIV-treated groups as compared with the untreated controls (final body weight, shown in Table 1); however, no changes were observed between the NIV-alone and NIV+SMTP-7 groups (Table 1). With respect to the kidney weight at necropsy, absolute and relative kidney weights showed no significant changes between the untreated controls and NIV-treated groups and also between the NIV-alone and NIV+SMTP-7 groups (Table 1).

In Experiment 2, no deaths or clinical signs occurred during the animal study. No significant changes were observed in food intake and water consumption between the untreated controls and NIV-treated groups and also between the NIV-alone and NIV+SMTP-7 groups (data not shown). From week 3 of treatment with NIV through to necropsy, we observed a significant decrease in body weight in both NIV-treated groups as compared with the untreated controls (final body weight, shown in Table 1). There was a significant decrease in the body weight of the NIV+SMTP-7 group as compared with the NIV-alone group beginning two weeks before necropsy (final body weight, shown in Table 1). With respect to the kidney weight at necropsy, there was no difference in absolute weight between the untreated controls and NIV-treated groups or between the NIV-alone and NIV+SMTP-7 groups (Table 1). On the other hand, a significant increase in the relative kidney weight was observed in the NIV+SMTP-7 group as compared with the NIV-alone group due to the decreased final body weight.

Serum immunoglobulin concentrations

In both Experiment 1 and Experiment 2, the serum IgA concentration was significantly increased in both NIV-treated groups compared with the untreated controls; however, the serum IgG levels were unchanged with NIV treatment (Table 2). Both serum IgA and IgG levels in the

Table 1. Final Body and Kidney Weights in Experiments 1 and 2

Experiment 1		Untreated controls	NIV-alone	NIV+SMTP-7
No. of animals examined		8	11	13
Final body weight (g)		23.41 ± 1.48 ^a	22.18 ± 1.33**	19.97 ± 1.44**
Kidney weights	Absolute (g)	0.309 ± 0.021	0.292 ± 0.024	0.265 ± 0.028
	Relative (g/g body weight)	0.013 ± 0.000	0.013 ± 0.001	0.013 ± 0.001
Experiment 2		Untreated controls	NIV-alone	NIV+SMTP-7
No. of animals examined		8	12	14
Final body weight (g)		26.00 ± 2.18	23.91 ± 0.95**	22.35 ± 1.74**†
Kidney weights	Absolute (g)	0.349 ± 0.016	0.333 ± 0.020	0.331 ± 0.045
	Relative (g/g body weight)	0.014 ± 0.001	0.014 ± 0.001	0.015 ± 0.001†

^a Mean ± SD. * P<0.05 vs. untreated controls (Tukey's test). † P<0.05 vs. NIV-alone group (Tukey's test). NIV, nivalenol; SMTP, *Stachybotrys microspora* triprenyl phenol.

Table 2. Serum IgA and IgG Levels in Experiments 1 and 2

Experiment 1		Untreated controls	NIV-alone	NIV+SMTP-7
No. of animals examined		7	10	13
Serum IgA (mg/dl)		45.29 ± 4.12 ^a	74.07 ± 15.98**	69.37 ± 11.25**
Serum IgG (mg/dl)		149.86 ± 29.86	140.44 ± 24.42	152.62 ± 31.04
Experiment 2		Untreated controls	NIV-alone	NIV+SMTP-7
No. of animals examined		8	12	14
Serum IgA (mg/dl)		51.53 ± 11.43	116.11 ± 44.94**	112.06 ± 29.65**
Serum IgG (mg/dl)		208.33 ± 49.48	199.22 ± 40.42	216.69 ± 36.86

^a Mean ± SD. ** P<0.01 vs. untreated controls (Tukey's test). NIV, nivalenol; SMTP, *Stachybotrys microspora* triprenyl phenol.

NIV+SMTP-7 group showed no significant changes when compared with the NIV-alone group.

Histopathology and immunofluorescence analysis

In both Experiment 1 and Experiment 2, kidneys in the NIV-treated groups did not reveal any apparent histopathological changes.

In Experiment 1, the immunofluorescence signal of IgA in the glomerular mesangial area in the NIV-treated groups apparently increased compared with the untreated controls (Fig. 2). Both scores for immunofluorescence intensity and quantitative signal intensity data for IgA immunoreactivity in the mesangial area showed significant increases in the NIV-treated groups as compared with the untreated controls. While scores for immunofluorescence intensity of IgA were statistically nonsignificant between the NIV-alone and NIV+SMTP-7 groups (Fig. 2A), quantitative signal intensity data for IgA immunoreactivity in glomeruli showed a significant decrease as a result of treatment with SMTP-7 as compared with NIV-alone (Fig. 2B).

In Experiment 2, the immunofluorescence signal of IgA in the glomerular mesangial area in the NIV-treated groups apparently increased compared with the untreated controls (Fig. 3). Both scores for immunofluorescence intensity and quantitative signal intensity data for IgA immunoreactivity in the mesangial area showed significant increases in the NIV-treated groups as compared with the untreated controls; however, they were statistically nonsignificant between the NIV-alone and NIV+SMTP-7 groups (Fig. 3A, B).

Discussion

In the present study, we investigated the effect of SMTP-7 on the development of IgAN using a mouse IgAN model induced by NIV in BALB/c mice. NIV has been shown to stimulate T-helper (Th) 2 cells to produce cytokines that may eventually lead to IgA hyperproduction²⁰. However, we revealed that SMTP-7 in this study did not affect the serum concentrations of IgA or IgG in both Experiment 1 and Experiment 2, suggesting no effect of SMTP-7 on IgA production. On the other hand, we found that co-treatment of SMTP-7 with NIV for 8 weeks slightly reduced the deposition of IgA in the glomeruli in Experiment 1. This result suggests that SMTP-7 has a potential to decrease the progression of IgAN induced by NIV through inhibition of the local accumulation of IgA in the glomerular mesangium. On the other hand, we could not detect any inhibitory effect of SMTP-7 on the already deposited IgA in the glomerular mesangium in Experiment 2, suggesting that SMTP-7 may not be effective for ameliorating advanced IgAN.

With regard to the deposition of IgA in the glomerular mesangium, virus-induced experimental IgAN models have shown that BALB/c mice are genetically prone to shift Th2-immune responses and that this T cell cytokine polarity is a determinant of reduction in terminal galactosylation and sialylation of IgA^{21,22}, which are recognized as important pathogenic factors in glomerular IgA deposition^{23,24}. We have shown that BALB/c mice are a sensitive strain for induction of NIV-induced glomerular deposition of IgA¹⁴. These find-

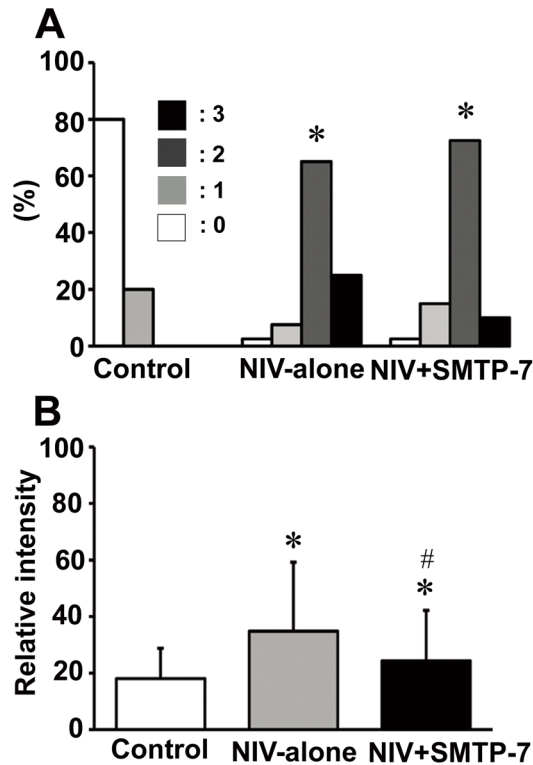
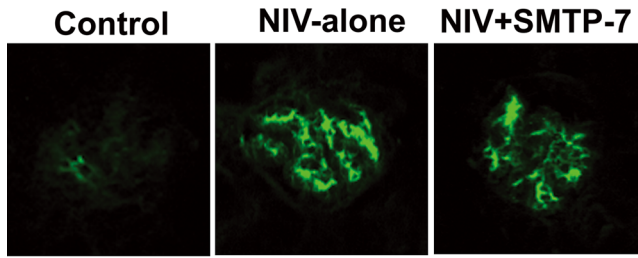


Fig. 2. Cotreatment effect of SMTP-7 on NIV-induced glomerular IgA deposition in the kidneys of female BALB/c mice in Experiment 1. A. The immunofluorescence intensity for IgA in the glomerular mesangial area in each group was scored as 0 (none), 1 (slight), 2 (moderate) or 3 (strong). * $P < 0.05$ vs. untreated controls (Mann-Whitney U test). B. Quantitative signal intensity data for IgA deposition in the glomerular mesangial area in each group. Values are expressed as means \pm SD. * $P < 0.05$ vs. untreated controls; # $P < 0.05$ vs. NIV-alone group (Tukey's test).

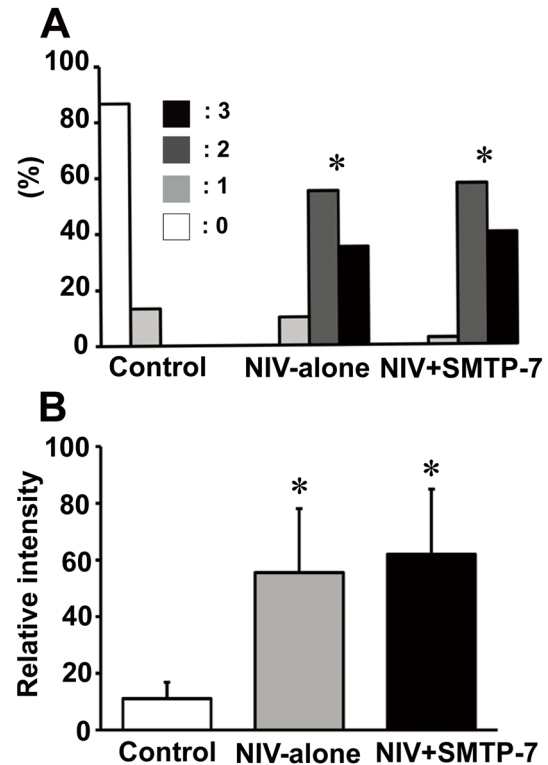
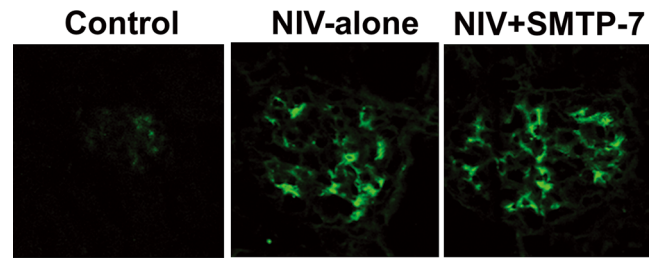


Fig. 3. Effect of SMTP-7 on already deposited IgA by NIV treatment in the kidneys of female BALB/c mice in Experiment 2. A. The immunofluorescence intensity for IgA in the glomerular mesangial area in each group was scored as 0 (none), 1 (slight), 2 (moderate) or 3 (strong). * $P < 0.05$ vs. untreated controls (Mann-Whitney U test). B. Quantitative signal intensity data for IgA deposition in the glomerular mesangial area in each group. Values are expressed as means \pm SD. * $P < 0.05$ vs. untreated controls (Tukey's test).

ings may suggest that SMTP-7 prevents NIV-induced alteration in Th2-immune responses for suppression of glomerular IgA deposition; however, the suppressive effect is mild. In a mouse model of cerebral infarction, SMTP-7 dose-dependently reduced the infarction area, neurological score and edema percentage by suppressing the expression of inflammatory cytokines produced by macrophages, such as IL-1 β , TNF- α , IL-6¹⁷. Although we could not obtain direct evidence that SMTP-7 prevents NIV-induced alteration in Th2-immune responses, influence of SMTP-7 on proinflammatory cytokine expression may cause alteration of T-cell immunity for protection of NIV-induced glomerular IgA-deposition.

Although changes were statistically nonsignificant in

Experiment 1, SMTP-7 treatment resulted in the slight decreases in body weight in mice in the present study. Because we did not examine other toxicity parameters, we could not determine the cause of this body weight decrease; however, there were no histopathological alterations in the kidneys in these animals.

In conclusion, we found the evidence that SMTP-7 has a potential to decrease the progression of IgAN induced by NIV through inhibition of the local accumulation of IgA in the glomerular mesangium, while it was ineffective in suppressing IgA production. We also found that SMTP-7 may not be effective in ameliorating advanced IgAN.

Acknowledgments: We thank Mrs. Shigeko Suzuki for her technical assistance in preparing the histological specimens. This work was supported by Health and Labour Sciences Research Grants (Research on Food Safety) from the Ministry of Health, Labour and Welfare of Japan. All authors disclose that there are no conflicts of interest that could inappropriately influence the outcome of the present study.

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