

A small amount of tetrachloroethylene ingestion from drinking water accelerates antigen-stimulated allergic responses

Makoto Seo^{a,*}, Takeo Yamagiwa^a, Ryo Kobayashi^a, Koji Ikeda^a, Masahiko Satoh^a, Naoki Inagaki^b, Hiroichi Nagai^c, Hisamitsu Nagase^a

^aLaboratory of Hygienics, Gifu Pharmaceutical University, Gifu, Japan

^bLaboratory of Pharmacology, Gifu Pharmaceutical University, Gifu, Japan

^cLaboratory of Clinical Pharmacology, Gifu Pharmaceutical University, Gifu, Japan

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Abstract

Previously, we observed that tetrachloroethylene (perchloroethylene, PCE) increased histamine release and inflammatory mediator production from antigen-stimulated mast cells. In this study, we examined the enhancing effect of low concentrations of PCE in drinking water on antigen-stimulated allergic responses. After exposure of Wistar rats to PCE in drinking water for 2 or 4 weeks, we performed a passive cutaneous anaphylaxis (PCA) reaction. PCE exposure for 4 weeks enhanced PCA reaction in a dose-dependent manner. In pathological studies, PCE exposure for 2 weeks exacerbated inflammation characterized by infiltration of lymphocytes and accumulation of mast cells around the vessel. Non-purified mast cells (NPMCs) from rats treated with 1 mg/L PCE in drinking water for 2 weeks increased antigen-stimulated histamine release. Furthermore, the leukocytes of rats treated with PCE in drinking water for 4 weeks showed increased interleukin (IL)-4 expression. The mechanism of enhancing the PCA reaction is assumed to be that PCE increases IL-4 production and PCE causes T helper (Th) 1/Th2-type helper T-cell imbalance and increases histamine release from excessively accumulated mast cells. The results suggest that the intake of PCE in drinking water, even at a low concentration, leads to the initiation and acceleration of allergic diseases.

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Introduction

The prevalence rate of allergic disorders, such as bronchial asthma and atopic dermatitis, is clearly increasing in industrial areas and countries (Beasley

et al. 2003). Recent reports suggest that environmental pollutants, such as diesel exhaust particles and formaldehyde, are closely related to the increase in allergic diseases (Wantke et al. 1996; Takano et al. 1997; Terada et al. 1999; Strachan 2000; Etzel 2003). These pollutants have been shown to induce the production of inflammatory mediators, enhance IgE production and increase histamine release from mast cells (Takenaka et al. 1995; Saneyoshi et al. 1997; Takizawa et al. 1999).

Tetrachloroethylene (perchloroethylene, PCE) is a volatile organic compound widely used in industry as a dry-cleaning and metal-degreasing agent, in paint

Abbreviations: DNP, dinitrophenol; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IFN, interferon; IL, interleukin; NPMCs, non-purified mast cells; PCA, passive cutaneous anaphylaxis; PCE, tetrachloroethylene; PMCs, purified mast cells; Th, T helper.

*Corresponding author. Tel.: +81 58 237 8579;
fax: +81 58 237 5979.

E-mail address: mkt.s.lev5060@gmail.com (M. Seo).

removers and as a component of adhesives and lubricants. As a consequence of this widespread use, it is commonly detected as an environmental contaminant of groundwater, surface water and soil (Josephson 1986; Westrick et al. 1984). Chronic exposure to PCE is accompanied by many severe toxicological and pathological problems. The toxic effects of PCE exposure are associated with disturbances in the central nervous system and changes in the parenchymal organs in the liver and kidneys (Lawrence and Jean 2001; Wang et al. 2002). PCE exposure has also shown mutagenic and carcinogenic effects in some animals (Lawrence and Jean 2001). Immunological parameters in dry-cleaning workers exposed to PCE were changed, such as alpha 2-microglobulin, percentage of T-lymphocytes, and total leukocytes count (Andrys et al. 1997). Natural killer activity of rat cells exposed to PCE was inhibited (Schlichting et al. 1992).

We have previously reported that PCE increases histamine release and inflammatory mediator production from antigen-stimulated mast cells *in vitro* (Seo et al. 2008), but there are no reports of *in vivo* studies about the effect of PCE in drinking water on antigen-stimulated allergic responses. In the present study, we treated Wistar rats with low concentrations of PCE in drinking water for 2 or 4 weeks in order to examine the enhancing effects of PCE on antigen-stimulated histamine release from non-purified rat peritoneal mast cells (NPMCs) and passive cutaneous anaphylaxis (PCA) reaction. Further, we investigated histological changes of the skin and immune tissues from the rats treated with PCE in drinking water, and we measured T helper (Th) 1 and Th2 cytokine mRNA expression of the rat leukocytes treated with PCE in drinking water.

Materials and methods

Reagents and animals

PCE (purity 98%) was purchased from Nacalai Tesque Co. Ltd. (Kyoto, Japan). A rat anti-dinitrophenol (DNP) monoclonal IgE antibody-producing cell line, REC, established in Kissei Pharmaceutical Co. Ltd. (Hotaka, Japan), was maintained. The culture supernatant of REC was used as a source of IgE antibody. The IgE antibody titer of the preparation estimated by homologous PCA was 1:4000 or greater. DNP-conjugated bovine serum albumin (DNP-BSA) was prepared according to the method that was previously reported (Eisen et al. 1953). The number of DNP residues introduced was 13 per BSA molecule. Male Wistar rats weighing 250–300 g were purchased from Japan SLC Inc. (Hamamatsu, Japan). They were housed three per cage and maintained on a 12-h light:dark cycle.

Water and a pelleted diet were supplied *ad libitum* before PCE treatment. Experiments were undertaken following the guideline for the care and use of experimental animals produced by the Japanese Association for Laboratory Animal Science in 1987.

Animals and PCE treatments

A 10 g/L PCE stock solution was prepared in dimethyl sulphoxide (DMSO). This stock solution was diluted with distilled water, and 0.01 and 1 mg/L PCE solutions were prepared, and used as drinking water. The final concentration of DMSO was 0.01% (v/v) in the experimental animals' drinking water. Preliminary tests showed that this concentration of DMSO, on its own, had no effect on the animals. Therefore distilled water, rather than water containing 0.01% (v/v) DMSO, was used for the control vehicle group of animals in our experiments.

Eight-week-old Wistar rats were treated with PCE in drinking water at a concentration of 0.01 or 1 mg/L for 2 or 4 weeks. The water was changed every other day to ensure dose maintenance.

Measurements of mast cell degranulation

Rats were treated with PCE in drinking water for 2 weeks. Before 48 h of the end of the treatment period, anti-DNP monoclonal IgE antibody was diluted 1:200 with Dulbecco's PBS, and 2 mL was injected into rats intraperitoneally to sensitize peritoneal mast cells. After treatment with PCE, NPMCs were collected from the rat peritoneal cavity after injecting Tyrode solution (137 mM NaCl, 2.7 mM KCl, 1.6 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES, 0.05% gelatin, 0.1% glucose, 0.41 mM NaH₂PO₄, pH 7.4), and centrifuged at 45 × g for 5 min. NPMCs were resuspended in Tyrode solution, and then used for histamine release assay. Purified mast cells (PMCs) were purified from NPMCs according to the method described by Inagaki et al. (1994). The content of PMCs was greater than 90% in all cases.

The suspension of NPMCs and PMCs ($1-3 \times 10^5$ cells/mL) were stimulated with 1 µg/mL DNP-BSA in Tyrode solution, and the cells were incubated at 37 °C for 15 min for antigen-stimulated histamine release.

Supernatants were collected and histamine content in supernatants was determined according to previous method (Sato et al. 1998). Histamine release (% of total) was indicated as the ratio of the fluorescence intensity of histamine content from antigen-stimulated mast cells to that of total histamine content of mast cells.

Histological evaluation and measurement of lymphocytes and mast cells in dermis

After treatment with PCE in drinking water for 2 weeks, the skin was fixed in 10% neutral-buffered formalin, and embedded in paraffin. After treatment with PCE in drinking water for 4 weeks, the immune tissues, such as spleen, thymus, cervical lymph nodes and mesenteric lymph nodes, were removed from rats and wet weights of them were measured. These tissues were fixed in 10% neutral-buffered formalin, and embedded in paraffin. Serial sections (4 μ m thick) were stained with hematoxylin–eosin or Alcian blue staining.

Histological analyses were performed using a microscope (Olympus). The numbers of lymphocytes infiltrating the dermis were counted per unit area (1 mm²), and the numbers of mast cells accumulated perivascularly were counted per blood vessel.

PCA reaction

Before 48 h of each treatment endpoint (2 and 4 weeks), 0.1 mL of anti-DNP IgE diluted to 1:1000 or 1:4000 was injected subcutaneously into both abdominal sides. After treatment with PCE, 1 mL of antigen–Evans blue solution (1 mg of DNP-BSA and 5 mg of Evans blue were dissolved in 1 mL of saline) was injected into the tail vein. The rats were killed after 30 min, and skin with blue spots was removed.

The extraction of Evans blue was performed according to Katayama et al. (1978). In brief, the pigment spot was placed in a test tube and incubated overnight at 37 °C with 1 mL of 1 N KOH, then 9 mL of 0.6 N H₃PO₄–acetone (5:13) was added and the pigment was extracted by mixing. After centrifugation, absorbance of the supernatant was measured at 620 nm.

Cytokine profile analysis

After treatment with PCE for 4 weeks, total RNA of whole blood collected from rats was extracted with an AquaPure RNA Isolation kit (BioRad). One microgram of total RNA from each sample was reverse transcribed using Oligo (dT) primers and Superscript II reverse transcriptase according to the manufacturer's instructions (Invitrogen).

PCR amplification was performed with Ex Taq Polymerase (Takara Bio Inc.) using the IQTM-Cycler (BioRad). The primer sequences and annealing temperature of IL-4, IFN- γ and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were as follows: IL-4 (Accession no. X16058; forward primer, 5'-TCT CAC GTC ACT GAC TGT A-3'; reverse primer, 5'-CTT TCA GTG TTG TGA GCG T-3'; annealing temperature, 53 °C; product size, 406 bp), IFN- γ (Accession no.

AF010466; forward primer, 5'-AGA GCC TCC TCT TGG ATA TCT GG-3'; reverse primer, 5'-GCT TCC TTA GGC TAG ATT CTG GTG-3'; annealing temperature, 60 °C; product size, 309 bp), GAPDH (Accession no. X02231; forward primer, 5'-GCA TGG CCT TCC GTG TTC CTA C-3'; reverse primer, 5'-ACT CCT TGG AGG CCA TGT AGG C-3'; annealing temperature, 62 °C; product size, 318 bp). The PCR reaction was performed under the following conditions: 94 °C, 30 s; annealing temperature of each gene, 30 s; and 72 °C, 1 min, for 35 cycles. The PCR products were electrophoresed in a 1% agarose gel and visualized by ethidium bromide staining. The PCR products were semi-quantitatively analyzed with an image analyzer (Densitograph, ATTO). The relative expression intensity was calculated according to the following formula: IL-4 mRNA or IFN- γ mRNA/GAPDH mRNA in each sample.

Statistical analysis

Data are shown as the mean $\pm$ S.E. Statistical analyses were performed with StatView (SAS Institute, version 5.0). Fisher's protected least significant difference test or Scheffe's *F*-test was applied, and a *p*-value < 0.05 was considered significant.

Results

Daily drinking volume

The volume of drinking water consumed by the PCE treated groups on each day was not significantly different from that consumed by vehicle group (data not shown). Each group of rats consumed 23.0 mL/day as an average of drinking water volume. These doses calculated to an average dose of 0.23 μ g/day (0.01 mg/L PCE treatment group) or 23.0 μ g/day (1 mg/L PCE treatment group), respectively.

PCE in drinking water for 2 weeks enhanced histamine release from NPMCs and PMCs

To evaluate the enhancing effect of PCE treatment in drinking water for 2 weeks on antigen-stimulated histamine release from NPMCs and PMCs, we separated NPMCs and PMCs from rats and examined antigen-stimulated histamine release from these cells. The results are shown in Fig. 1. PMCs treated with 1 mg/L PCE in drinking water for 2 weeks significantly enhanced antigen-stimulated histamine release (Fig. 1A). Similarly, NPMCs treated with 1 mg/L PCE in drinking water for 2 weeks significantly enhanced antigen-stimulated histamine release (Fig. 1B).

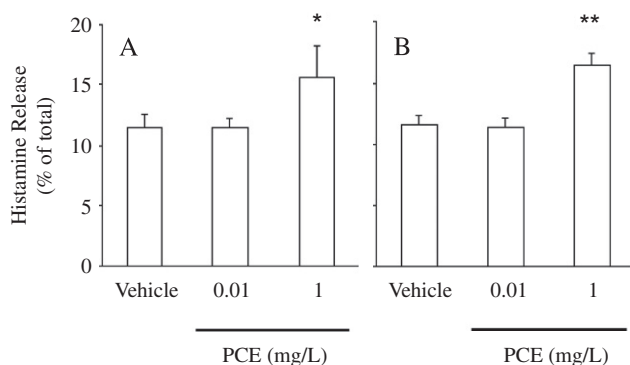


Fig. 1. Effect of PCE in drinking water for 2 weeks on histamine release from antigen-stimulated NPMCs (A) and PMCs (B). The percent of histamine release was calculated as the ratio of fluorescence intensity of a test sample to that of total histamine. Data are expressed as the mean $\pm$ S.E. * $p < 0.05$, ** $p < 0.01$.

PCE aggravates histological changes in the skin

To evaluate histological changes in the skin lesion by PCE treatment in drinking water for 2 weeks, we performed hematoxylin–eosin staining, with the results shown in Fig. 2. Treatment with 0.01 and 1 mg/L PCE in drinking water for 2 weeks significantly enhanced the infiltration of lymphocytes into dermal skin lesions in comparison with the vehicle (Fig. 2A–D, Fig. 2A: $p < 0.01$ for 0.01 or 1 mg/L PCE vs. vehicle).

Correspondingly, the accumulation of mast cells perivascularly showed parallel changes (Fig. 2E–H, Fig. 2E: $p < 0.01$ for 0.01 or 1 mg/L PCE vs. vehicle).

PCE exposure in drinking water for 2 or 4 weeks enhanced PCA reaction

To evaluate the effect of PCE in drinking water on type I allergic reaction, we examined the PCA reaction. Treatment with PCE in drinking water for 2 weeks slightly enhanced the PCA reaction (Fig. 3A); however, treatment with 1 mg/L PCE in drinking water for 4 weeks significantly enhanced the PCA reaction compared with the vehicle (Fig. 3B: enhancing ratio; 1.3–1.5).

PCE exposure induced an imbalance of immune tissues and Th1/Th2 cytokine secretion

To evaluate histological changes in immune tissues by PCE treatment in drinking water, we removed the spleen, thymus, cervical lymph nodes and mesenteric lymph nodes, and their wet weights were measured. It was shown that the wet weights of mesenteric lymph nodes in the group of 0.01 and 1 mg/L PCE treatment in

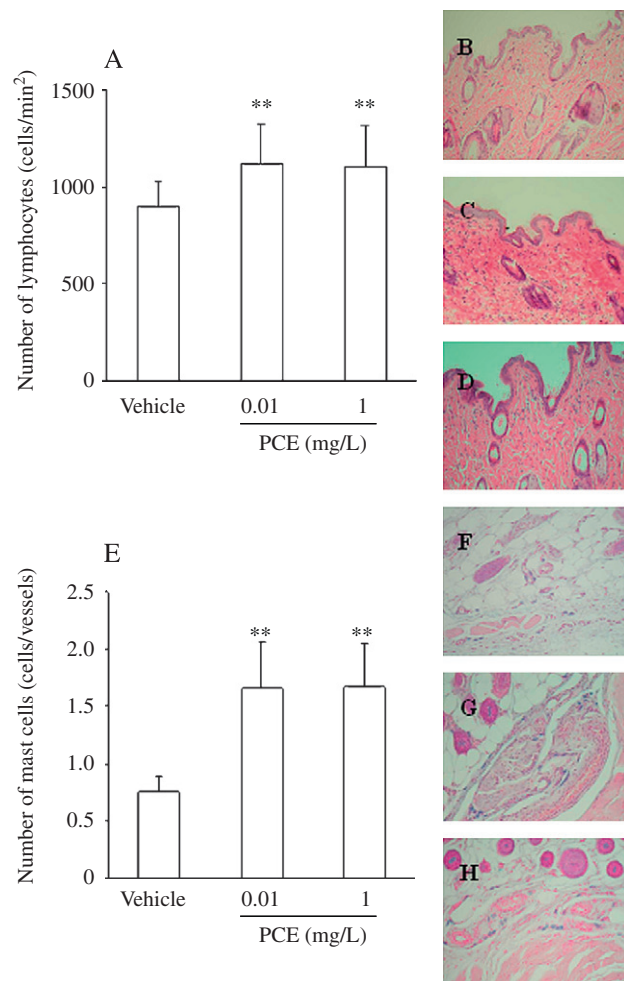


Fig. 2. Histological changes in the skin of rats treated with PCE in drinking water for 2 weeks. The infiltration of lymphocytes (A) and accumulation of mast cells (E) were evaluated as the number of cells per unit. Vehicle (B, F), 0.01 mg/L PCE in drinking water (C, G) or 1 mg/L PCE in drinking water (D, H) was shown with hematoxylin–eosin staining (B–D) or Alcian blue staining (F–H). Data are expressed as the mean $\pm$ S.E. ** $p < 0.01$.

drinking water were significantly increased compared with the vehicle (Fig. 4A). We then examined histological changes of mesenteric lymph nodes with hematoxylin–eosin staining; the results are shown in Fig. 4B, C and D. Treatment with PCE in drinking water enlarged lymphoid nodules and clearly showed their germinal centers compared with the vehicle.

To evaluate the effect of PCE treatment in drinking water on Th1/Th2 cytokine mRNA expression, we examined IL-4 and IFN- γ mRNA expression in lymphocytes from whole blood of rats. The results are shown in Fig. 5. Treatment with 1 mg/L PCE in drinking water increased IL-4 mRNA expression (Fig. 5A; increasing ratio compared with the vehicle, 1.3), but there was no change in IFN- γ mRNA expression (Fig. 5B).

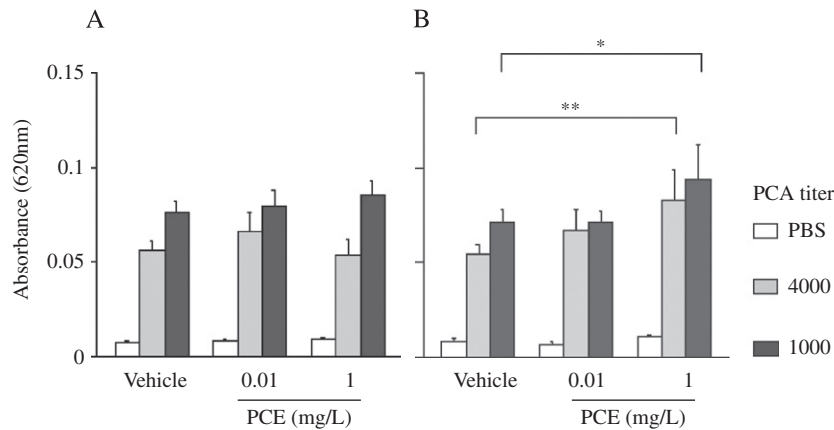


Fig. 3. Effect of PCE in drinking water for 2 or 4 weeks on PCA reaction. Before 48 h of the end of treatment for 2 weeks (A) or 4 weeks (B), 0.1 mL of rat anti-DNP monoclonal IgE antibody diluted to 1:1000 or 1:4000 was injected intradermally. Antigen–Evans blue solution was injected into the tail vein. Skin with blue spots was removed, and the supernatant of Evans blue was measured. Data are expressed as the mean $\pm$ S.E. * p < 0.05, ** p < 0.01.

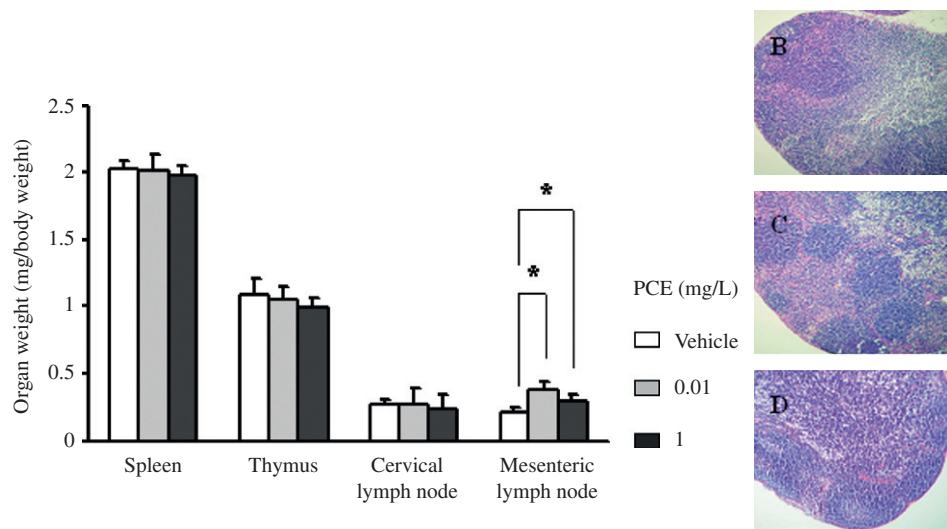


Fig. 4. Histological changes in mesenteric lymph nodes treated with PCE in drinking water for 4 weeks. We evaluated the wet weight of immune tissues treated with PCE in drinking water (A). Mesenteric lymph nodes of the vehicle (B), 0.01 mg/L PCE in drinking water (C) or 1 mg/L PCE in drinking water (D) are shown with hematoxylin–eosin staining (original magnification: $\times$ 100). Data are expressed as the mean $\pm$ S.E. * p < 0.05.

Discussion

The main findings of this study are that treatment with PCE in drinking water enhanced antigen-stimulated allergic reaction. Treatment with PCE in drinking water for 2 weeks caused hyper responsiveness in antigen-induced histamine release from mast cells. And treatment with PCE in drinking water for 2 weeks caused histological changes in the skin, such as infiltration of lymphocytes and accumulation of mast cells perivascularly. Moreover, treatment with PCE in drinking water for 4 weeks gave rise to the enhancing effect of PCA reaction. The mesenteric lymph nodes treated with PCE in drinking water for 4 weeks enlarged lymphoid nodule size and their germinal centers were

clearly observed. Furthermore, our results indicate that these enhancing effects were attributable to the IL-4 expression of the leukocyte.

PCE is widely used as a dry-cleaning and metal-degreasing solvent, and is a hazardous pollutant of water, air and soil. The main routes of potential human exposure to PCE are inhalation, dermal contact and ingestion from drinking water (Lawrence and Jean 2001). In this study, we used a low concentration of 0.01 mg/L PCE. This concentration is defined by Japanese environmental standard for water and Japanese drinking water quality guideline, and this guideline value of PCE is similar to the value of the WHO drinking water guidelines (World Health Organization 1996). The other testing concentration, 1 mg/L PCE, has

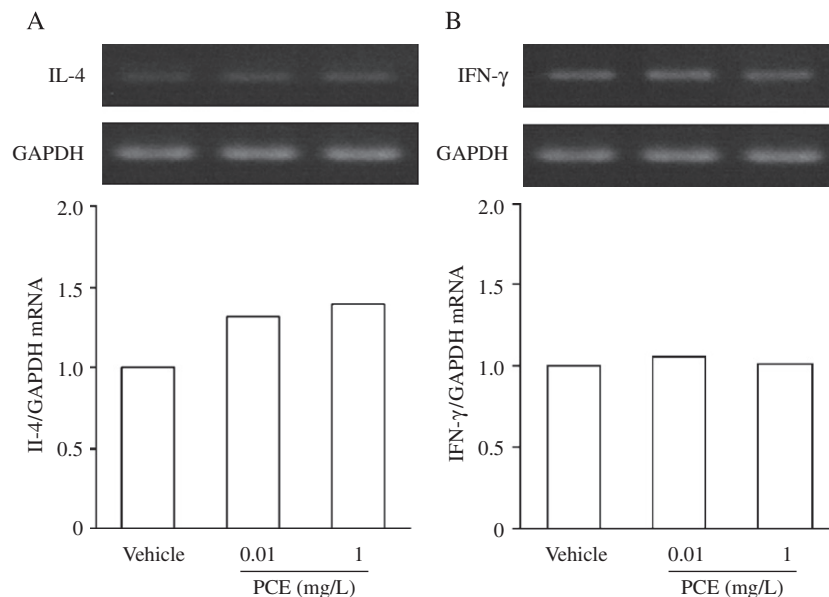


Fig. 5. Gel electrophoresis of RT-PCR products obtained from lymphocytes separated from rats treated with PCE in drinking water for 4 weeks. The PCR products were semi-quantitatively analyzed with an image analyzer. The relative expression intensity was calculated according to the following formula: IL-4 mRNA/GAPDH mRNA (A) or IFN- γ mRNA/GAPDH mRNA (B).

been detected in groundwater from contaminated areas (Giger and Molnar-Kubica 1978; Leschber et al. 1990); therefore, we could conceivably be exposed to these concentrations of PCE.

Our results showed that treatment with PCE in drinking water for 2 weeks enhanced histamine release from antigen-stimulated PMCs and NPMCs, induced the infiltration of lymphocytes into dermal skin lesions and accumulated mast cells perivascularly. Treatment with PCE in drinking water for 2 weeks slightly enhanced the PCA reaction, but treatment with 1 mg/L PCE in drinking water for 4 weeks significantly enhanced the PCA reaction. We consider that the enhancement mechanisms of the PCA reaction are the perivascular accumulation of mast cells and increased histamine release from mast cells associated with hyper reactivity of the antigen–antibody reaction, and the infiltration of lymphocytes in dermal skin lesion and increase of inflammatory cells in local lymph nodes induced the production of inflammatory cytokines. These factors may synergistically enhance type I allergic reaction.

IL-4 is a cytokine produced by Th2 cells and mast cells (Kobayashi et al. 2000). There are many reports that IL-4 induces the over-expression of Fc ϵ RI, which is an initiating molecule of the antigen–antibody reaction (Yamaguchi et al. 1999). We also consider that another enhancement mechanism may increase histamine release due to IL-4 mRNA expression on lymphocytes treated with PCE in drinking water for 4 weeks. In recent studies, it has been noted that T cells mainly induce an allergic reaction. There are two different types of helper T cells, Th1 and Th2 (Mosmann and Coffman 1989;

Romagnani 1995). Th1 produces IFN- γ and has inhibitory effects to exert an allergic reaction and, whereas Th2 produces IL-4, 5, 10 and 13, it plays a key role in exerting an allergic reaction in humoral immunity. It has been defined that allergic diseases are localized Th2 in the Th1/Th2 paradigm (Maggi 1998). There are many reports that cytokine profiles of T cells from allergic patients are biased toward Th2 (Kapsenberg et al. 1991; Parronchi et al. 1991; Del Prete et al. 1993); therefore, the balance between IFN- γ -producing Th1 cells and IL-4-producing Th2 cells is substantially important to induce allergic responsiveness. Our results show that PCE ingestion led to Th2 and enhanced the activation of antigen–antibody reaction on mast cells. Our results indicate that treatment with PCE ingestion forces the immune system to incline towards a Th2 response. In the future, the influence of PCE on the immune network should be examined.

In conclusion, we demonstrated the enhancing effect of PCE in drinking water on the PCA reaction and the hyper reactivity of antigen-stimulated mast cells. These results suggest that PCE ingestion causes inflammation (inflammatory states) of the skin and immune tissues. PCE ingestion also up-regulates IL-4 production, which likely determines the Th2 profile. The Th1/Th2 imbalance from PCE in drinking water will accelerate the increase in allergic diseases.

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