

Exposure to road traffic enhances allergic skin wheal responses and increases plasma neuropeptides and neurotrophins in patients with atopic eczema/dermatitis syndrome

Hajime Kimata

Department of Allergy, Ujitakeda Hospital, Uji-City, Kyoto, Japan

Received February 14, 2003 · Revision received July 17, 2003 · Accepted July 19, 2003

Abstract

The effect of exposure to road traffic was studied by sitting on chairs for 30 min beside a road with heavy wheeled traffic. Exposure to road traffic enhanced allergen-induced, but not histamine-induced, skin wheal responses in 26 patients with atopic eczema/dermatitis syndrome, while it had no effect on skin wheal responses in 26 normal subjects. Exposure to road traffic also increased plasma levels of substance P, vasoactive intestinal peptide, nerve growth factor, and neurotrophin-3 in patients with atopic eczema/dermatitis syndrome, while it had no effect on these plasma parameters in normal subjects. Collectively, exposure to road traffic may aggravate allergic diseases by enhancing allergic responses with concomitant increase in plasma levels of neuropeptides and neurotrophins.

Key words: Exposure to road traffic – house dust mite – skin wheal responses – substance P – vasoactive intestinal peptide – nerve growth factor – neurotrophin-3 – atopic eczema/dermatitis syndrome

Introduction

Although diesel exhaust particles enhance production of allergen-specific IgE and total IgE in human experimental systems (Diaz-Sanchez et al. 1997), the relation between exposure to road traffic and allergy remains to be elucidated (Hirsch et al. 2000; Nicolai, 2002; Wyler et al. 2000). Moreover, the direct effect of exposure to road traffic on allergic patients has not been reported. I and others have reported that plasma levels of substance P (SP), vasoactive intestinal peptide (VIP), nerve growth factor (NGF), and neurotrophin-3 (NT-3) were elevated in patients with atopic eczema/dermatitis

syndrome (AEDS) (Kimata, 2002b; Toyoda et al. 2002) or in patients with bronchial asthma (Noga et al. 2001). In addition, enhancement of allergic skin wheal responses is associated with increase in plasma levels of SP and VIP (Kimata, 2002b). This may be due to the fact that SP, VIP, and NGF trigger mast cell degranulation (Singh et al. 1999; Pearce and Thompson, 1986), or alternatively mast cells may produce SP, VIP, and NGF upon degranulation (Gulubova and Vodenicharov, 2001; Skaper et al. 2001; Toyoda et al. 2002). These results prompted me to study the effect of exposure to road traffic on skin wheal responses and plasma

Corresponding author: Dr. Hajime Kimata, Department of Allergy, Ujitakeda Hospital, 24-1, Umonji, Uji, Uji-City, Kyoto Prefecture, 611-0021, Japan. Phone: + 81 77425 2500, Fax: + 81 774 25 2353, E-mail: unitikah@m12.alpha-net.ne.jp

levels of neuropeptides and neurotrophins in patients with AEDS.

Materials and methods

Twenty six normal subjects (14 women and 12 men, mean age 25 years, range 21–34 years) and 26 patients with moderate AEDS (14 women and 12 men, mean age 26 years, range 22–36 years) by SCORAD index (Kunz et al. 1997) were studied after obtaining informed consent. All of the AEDS patients had skin symptoms all over the body, which were itchy and stressful, but none of them had allergic rhinitis or bronchial asthma. All of the AEDS patients were allergic to house dust mite (HDM) and cat dander as proven by skin prick test and positive serum allergen-specific IgE levels by RAST (mean 63.1 IU/ml for HDM and 30.7 IU/ml for cat dander). In contrast, none of them was allergic to latex or pollens (Japanese cedar, timothy, or ragweed), as proven by skin prick test (0.0 ± 0.0 mm) and serum allergen-specific IgE levels by RAST (< 0.34 IU/ml). All of the AEDS patients were treated with oral anti-allergic medication, oxatomide (60 mg/day), and skin care washing with povidone iodine followed by application of azulene ointment. Half-life of oxatomide was 5 h, and AEDS patients did not take oxatomide for 72 h prior to the study (Kimata, 2001a). Normal subjects had no allergic diseases, and they were not allergic as proven by skin prick test to HDM, cat dander and pollens (0 ± 0 mm) and negative serum allergen-specific IgE levels by RAST (< 0.34 IU/ml).

The study was conducted by crossover design. Randomly assigned 13 out of 26 normal subjects and 13 out of 26 AEDS patients first undertook exposure studies and after 2 weeks they undertook non-exposure studies. Alternatively, the other 13 normal subjects and 13 AEDS patients first undertook non-exposure studies and after 2 weeks they undertook exposure studies. In exposure studies, subjects sat on chairs for 30 min along a road with heavy traffic in the center of the city; in all 273–289 cars, including 71–74 trucks, passed during the study. In control non-exposure studies, normal subjects and AEDS patients sat on chairs for 30 min along the road with no traffic in the outskirts of the city; no cars passed during the study. All studies were conducted at 9:30 to 10:00 am.

Just before (9:30 am) and immediately after (10:00) each study, skin prick test were performed. Briefly, HDM, latex, Japanese cedar pollen, histamine (10 mg/ml) and control solution were applied to the middle of the volar part of the forearms, and 15 minutes later wheal responses were measured by staff who were blinded to the study (Kimata, 2002b). Consistent wheal responses were observed by this method (Kimata, 2001; Kimata, 2002a and 2002b). Simultaneously, blood was drawn and plasma levels of SP and VIP were measured by ELISA of Peninsula Laboratories INC. (California, USA), while plasma levels of NGF and NT-3 were measured by ELISA of Boehringer Mannheim Corp. (Mannheim, Germany) by staff who were blinded to the study.

In addition, I have also studied the effect of exposure to road traffic on skin wheal responses in 20 patients with bronchial asthma having cat allergy (13 women and 7 men, mean age 28 years, range 22–35 years) and in 20 patients with seasonal allergic rhinitis (11 women and 9 men, mean age 24 years, range 21–30 years). All of the patients with bronchial asthma were allergic to HDM and cat dander, but not to Japanese cedar pollen, while all of the patients with allergic rhinitis were allergic to Japanese cedar pollen, but not to HDM or cat dander as proved by skin prick test and serum allergen-specific IgE by RAST. Patients with bronchial asthma or patients with allergic rhinitis sat on chairs for 30 min along the road with heavy traffic in the center of the city as above. In all 252 cars, including 65 trucks passed in the study of patients with bronchial asthma, and 263 cars, including 68 trucks passed in the study of patients with allergic rhinitis.

Statistical analysis was performed with the two-tailed Student's *t*-test. This study was approved by the Ethical Committee of our hospital.

Results

As shown in Figure 1A, in the control non-exposure study, wheal responses by allergens or histamines were not changed in normal subjects or AEDS patients. In contrast, although wheal responses by allergens or histamine were not changed in normal subjects after exposure to road traffic, wheal responses by HDM were significantly enhanced in AEDS patients (Figure 1B). Moreover, wheal responses to cat dander were also enhanced by exposure to road traffic (6.4 ± 0.3 mm before vs 9.4 ± 0.4 mm after), while those responses were not enhanced in the non-exposure study (6.6 ± 0.3 mm before vs 6.3 ± 0.3 mm after). This was not due to non-specific irritation of the skin, as wheal responses by histamine were not enhanced (Figure 1B), and no wheal responses were induced by latex, Japanese cedar pollen or control solution (0.0 ± 0.0 mm before vs 0.0 ± 0.0 mm after). In addition, no wheal responses were induced by timothy or ragweed to which AEDS patients were not sensitized (0.0 ± 0.0 mm). Enhancement of wheal responses by HDM was still significant 2 h after exposure (10.3 ± 0.6 mm) ($P < 0.01$), but not after 4 h (8.7 ± 0.4 mm).

As shown in Figure 2 and 3, plasma levels of SP (Figure 2A), VIP (Figure 2B), NGF, and NT-3 (Figure 3A and 3B) were elevated in AEDS patients compared with those in normal subjects as previously reported (Kimata, 2002a, 2002b; Noga et al. 2001; Toyoda et al. 2002). In the control non-exposure study, plasma levels of these parameters were unchanged in normal subjects and AEDS

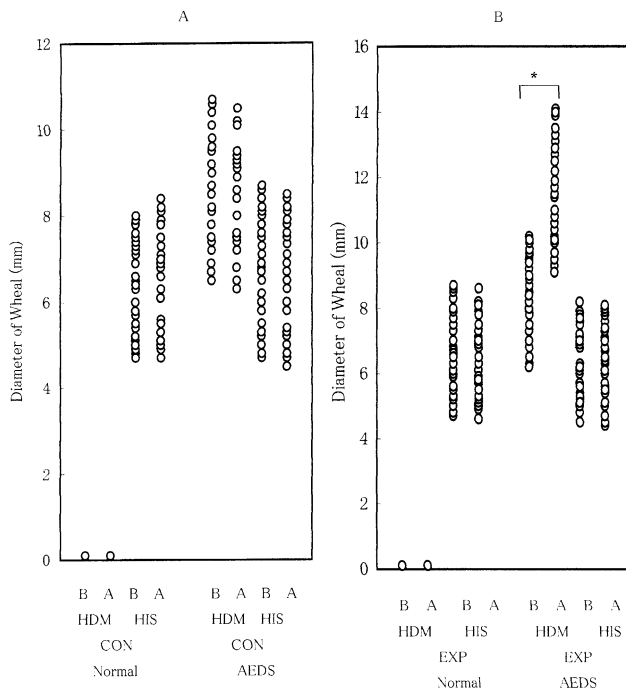


Fig. 1. Effect of exposure to road traffic on skin wheal responses. Panel A: In the control non-exposure study (CON), normal subjects (Normal) or patients with AEDS (AEDS) were not exposed to road traffic, and before (B) and after (A) 30 min, wheal response to house dust mite (HDM) or histamine (HIS) was measured. Panel B: In the exposure study (EXP), normal subjects (Normal) or patients with AEDS (AEDS) were exposed to road traffic, and before (B) and after (A) exposure, wheal response to house dust mite (HDM) or histamine (HIS) were measured. * Significant increase ($P < 0.001$).

patients (Figure 2A and Figure 3A and 3B). In contrast, exposure to road traffic increased plasma levels of SP (Figure 2A), VIP (Figure 2B), NGF, and NT-3 (Figure 3A and 3B) in AEDS patients, while it had no effect on these plasma parameters in normal subjects.

Exposure to road traffic also significantly enhanced skin wheal responses by HDM (7.8 ± 0.4 mm before vs 11.4 ± 0.5 mm after) ($P < 0.001$) or by cat dander (7.3 ± 0.4 mm before vs 10.6 ± 0.5 mm after) ($P < 0.001$), but not by Japanese cedar pollen (0.0 ± 0.0 mm before vs 0.0 ± 0.0 mm after) in patients with bronchial asthma. Similarly, exposure to road traffic significantly enhanced skin wheal responses by Japanese cedar pollen (8.1 ± 0.4 mm before vs 13.2 ± 0.6 mm after) ($P < 0.001$), but not by HDM (0.0 ± 0.0 mm before vs 0.0 ± 0.0 mm after) or cat dander (0.0 ± 0.0 mm before vs 0.0 ± 0.0 mm after) in patients with allergic rhinitis.

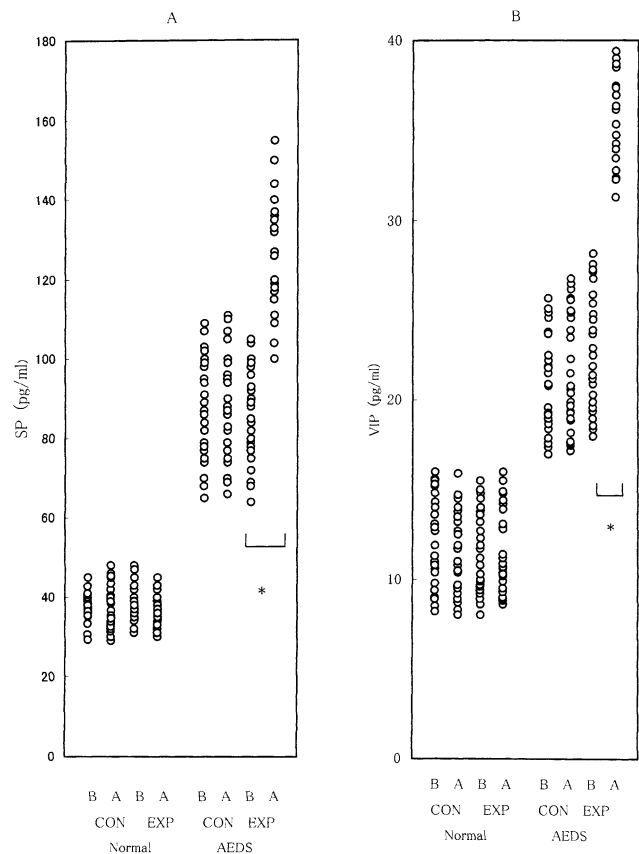


Fig. 2. Effect of exposure to road traffic on plasma SP and VIP levels. Normal subjects (Normal) or patients with AEDS (AEDS) were not exposed (control study, CON) or exposed to road traffic (exposure study, EXP), and before (B) and after (A), plasma SP (Panel A) or VIP (Panel B) levels were measured. * Significant increase ($P < 0.001$).

Discussion

I have demonstrated that exposure to road traffic enhanced allergen-induced skin wheal responses in AEDS patients. This was specific to those allergens to which patients were sensitized, as no wheal responses were induced by latex, Japanese cedar pollen, timothy or ragweed to which patients were not sensitized. Moreover, wheal responses by histamine were not enhanced. In addition, exposure to road traffic failed to induce wheal responses by allergens in normal subjects. These results indicate that exposure to road traffic enhances allergen-specific skin wheal responses in sensitized patients. Furthermore, exposure to road traffic increased plasma levels of SP, VIP, NGF, and NT-3 in AEDS patients, while it had no effect on these plasma parameters in normal subjects. It has been reported that SP, VIP, and NGF induce mast cell degranulation (Singh et al. 1999; Pearce and Thompson,

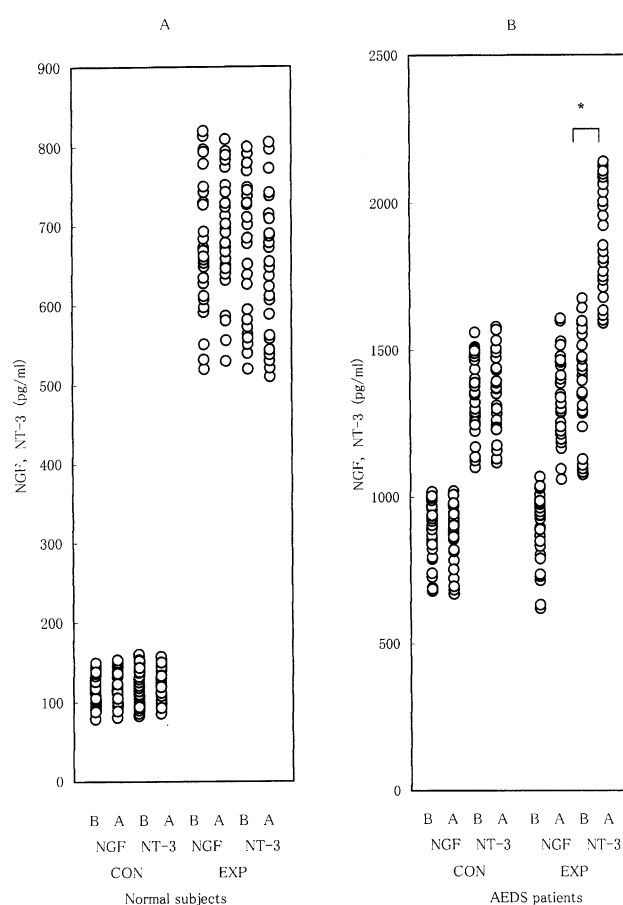


Fig. 3. Effect of exposure to road traffic on plasma NGF and NT-3 levels. Normal subjects (Panel A) or patients with AEDS (Panel B) were not exposed (control study, CON) or exposed to road traffic (exposure study, EXP), and before (B) and after (A), plasma NGF and NT-3 levels were measured. * Significant increase ($P < 0.001$).

1986). On the other hand, mast cells produced SP, VIP and NGF (Gulubova and Vodenicharov, 2001; Skaper et al. 2001; Toyoda et al. 2002). I have also reported that various stimuli enhanced allergen-induced skin wheal responses with concomitant increase in plasma levels of SP and VIP (Kimata, 2002b). However, there was no correlation between plasma levels of neuropeptides and wheal diameter of the skin prick test reaction. This study further demonstrated that plasma levels of NGF and NT-3 were increased in the enhancement of allergen-induced skin wheal responses. Although the role of NT-3 in allergy remains to be elucidated, serum levels of NT-3 were elevated in patients with bronchial asthma (Noga et al. 2001). In addition, mast cells expressed NT-3 (Gulubova and Vodenicharov, 2001; Skaper et al. 2001). These results indicate that NT-3 also may be involved in allergic responses.

The relation between exposure to road traffic and allergy has been reported previously. Exposure to road traffic increases allergy prevalence in children and adults (Diaz-Sanchez et al. 2003; Kramer et al. 2000; Nicolai, 2002; Polosa et al. 2002; Wyler et al. 2000). Here, I have demonstrated that exposure to road traffic enhanced allergen-induced skin wheal responses in adult AEDS patients. This is the first study showing that short-term exposure to road traffic in daily life enhances allergic responses with concomitant increase in plasma levels of SP, VIP, NGF, and NT-3 in allergic patients. It should be pointed out that previous epidemiologic studies indicate the effect of long-term exposure of road traffic and sensitization, while this study demonstrated enhancement of allergic responses by short-term exposure to road traffic. A study of the long-term exposure to road traffic is currently in progress. In addition, since the importance of mood on the variability of type I hypersensitivity responses has been reported (Kimata, 2001; Laidlaw et al. 1994), effect of psychological factors cannot be excluded. A large scale study is necessary to study the exact effect of exposure to road traffic on allergic diseases.

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