

Enhancement of allergic skin wheal responses in patients with atopic eczema/dermatitis syndrome by playing video games or by a frequently ringing mobile phone

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Abstract

Background Playing video games causes physical and psychological stress, including increased heart rate and blood pressure and aggression-related feelings. Use of mobile phones is very popular in Japan, and frequent ringing is a common and intrusive part of Japanese life. Atopic eczema/dermatitis syndrome is often exacerbated by stress. Stress increases serum IgE levels, skews cytokine pattern towards Th2 type, enhances allergen-induced skin wheal responses, and triggers mast cell degranulation via substance P, vasoactive intestinal peptide and nerve growth factor.

Materials and methods (1) In the video game study, normal subjects ($n = 25$), patients with allergic rhinitis ($n = 25$) or atopic eczema/dermatitis syndrome ($n = 25$) played a video game (STREET FIGHTER II) for 2 h. Before and after the study, allergen-induced wheal responses, plasma levels of substance P, vasoactive intestinal peptide and nerve growth factor, and *in vitro* production of total IgE, antihouse dust mite IgE and cytokines were measured. (2) In the mobile phone study, normal subjects ($n = 27$), patients with allergic rhinitis ($n = 27$) or atopic eczema/dermatitis syndrome ($n = 27$) were exposed to 30 incidences of ringing mobile phones during 30 min. Before and after the study, allergen-induced wheal responses, plasma levels of substance P, vasoactive intestinal peptide and nerve growth factor were measured.

Results Playing video games had no effect on the normal subjects or the patients with allergic rhinitis. In contrast, playing video games significantly enhanced allergen-induced skin wheal responses and increased plasma levels of substance P, vasoactive intestinal peptide and nerve growth factors in the patients with atopic eczema/dermatitis syndrome. Moreover, playing video games enhanced *in vitro* production of total IgE and anti-house dust mite IgE with concomitant increased production of IL-4, IL-10 and IL-13 and decreased production of IFN- γ and IL-12 in the patients with atopic eczema/dermatitis syndrome. However, exposure to frequently ringing mobile phones significantly enhanced allergen-induced skin wheal responses, plasma levels of substance P, vasoactive intestinal peptide and nerve growth factors in the patients with atopic eczema/dermatitis syndrome, but not in the normal subjects or the patients with allergic rhinitis.

Conclusion Playing video games enhanced allergic responses with a concomitant increased release of substance P, vasoactive intestinal peptide and nerve growth factor, and skewing of the cytokine pattern toward Th2 type in the patients with atopic eczema/dermatitis syndrome. In addition, exposure to frequently ringing mobile phones also enhanced allergic responses with a concomitant increased release of substance P, vasoactive intestinal peptide and nerve growth factor. Collectively, high technology causes stress, which in turn may aggravate symptoms of atopic eczema/dermatitis syndrome.

Keywords Atopic eczema/dermatitis syndrome, IgE, mobile phones, nerve growth factor, neuropeptides, skin wheal responses, video game.

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Introduction

Video games are now widely played, and it has been reported that playing video games causes physical and psychological stresses, including increased heart rate and blood pressure, sleep deprivation and aggression-related thoughts and feelings [1–4]. Use of mobile phones is very popular in Japan, and frequent ringing is a common and intrusive part of the Japanese life-style.

Atopic eczema/dermatitis syndrome (AEDS) is often exacerbated by stress. Stress increases serum IgE levels in patients with AEDS [5], skews the cytokine pattern towards Th2 type in patients with bronchial asthma [6,7], enhances allergen-induced skin wheal responses and *in vitro* IgE production in patients with allergic rhinitis (AR) [8], and triggers mast cell degranulation via substance P (SP) or vasoactive intestinal peptide (VIP) [9,10]. Nerve growth factor (NGF) also triggers mast cell degranulation, and stress enhances plasma NGF levels in healthy subjects [11–13]. Moreover, plasma SP, VIP and NGF levels are elevated in patients with AEDS [14,15]. In contrast, it has been previously reported that laughter caused by viewing a humorous video (Modern Times featuring Charlie Chaplin) reduced allergen-induced skin wheal responses in patients with AEDS [16]. These reports prompted the author to study whether playing video games or exposure to frequently ringing mobile phones modulates allergen-induced skin wheal responses, plasma levels of SP, VIP and NGF, and *in vitro* production of IgE and cytokines in atopic patients.

Methods

In the video game study, after obtaining informed consent, 25 normal subjects (13 women and 12 men, mean age 24 years, range 21–31 years), 25 patients with moderate AR (12 women and 13 men, mean age 23 years, range 21–32 years) by daytime nasal symptom score [17] and 25 patients with moderate AEDS (13 women and 12 men, mean age 24 years, range 21–33 years) by SCORAD index [18] were studied. In the mobile phone study, after obtaining informed consent, 27 normal subjects (14 women and 13 men, mean age 35 years, range 22–42 years), 27 patients with mild AR (14 women and 13 men, mean age 32 years, range 21–41 years) and 27 patients with mild AEDS (14 women and 13 men, mean age 33 years, range 23–44 years) were studied. All of the AR patients and AEDS patients were allergic to both house dust mite (HDM) and Japanese cedar pollen (JCP), but not to latex.

Patients with AR were treated with oral antiallergic medication, oxatomide (60 mg day⁻¹) (Kyowa Hakko, Industries, Ltd. Osaka, Japan), while patients with AEDS were treated with oxatomide (60 mg day⁻¹) and skin care, including washing with povidone iodine and application of the nonsteroidal anti-inflammatory ointment, azulen. Half-life of oxatomide was 5 h [19]. They did not take oxatomide for 72 h before the study, thus oxatomide was not able to

modulate the skin wheal responses and plasma parameters measured.

In the video game study, all of the subjects began to play the video game (STREET FIGHTER II) at 09:30 h and before (09:00 h), and after playing for 2 h (11:30 h), blood was drawn and skin prick tests were performed using HDM, JCP and latex allergen, histamine (10 mg mL⁻¹) as well as control solution, and 15 min later wheal sizes were measured by medical staff who were blind to the study [16]. All of the normal subjects and patients were unfamiliar with this type of video game. Mononuclear cells were separated from the blood, and they were cultured ($2 \times 10^5/0.2$ mL well⁻¹) with HDM allergen (0.1 ng mL⁻¹) in DME medium supplemented with Ham's nutrient (DMA/F-12 G, Sigma Chemical Co., St. Louis, MO) for 14 days, and production of total IgE and anti-HDM IgE was measured as previously reported [20,21]. In addition, mononuclear cells were cultured ($2 \times 10^5/0.2$ mL well⁻¹) with HDM allergen (100 ng mL⁻¹) for 5 days, and production of IL-4, IL-10, IL-12, IL-13 and IFN- γ was measured by ELISA (R & D Systems, Inc. Minneapolis, MN) [20]. Plasma levels of SP, VIP and NGF were measured by ELISA of Peninsula Laboratories Inc. (Belmont, CA) and Boehringer Mannheim Corp. (Mannheim, Germany), respectively, according to the manufacturers' protocol.

In the mobile phone study, all the subjects began to view a 30-min non-humorous video featuring weather information at 09:30 h, while mobile phones (Toshiba C451T) rang every minute. The ringing was stopped after 10 s. Thus, subjects were exposed to 30 incidents of ringing during 30 min. The weather information video was the same as in the previous study [16]. Before and after the study, blood was drawn and skin prick tests were performed, and plasma parameters and skin wheal responses were measured as in the video game study. Statistical analysis was performed with the Student's two-tailed *t*-test.

Results

As shown in Table 1, playing video games had no effect on wheal responses or plasma levels of SP, VIP and NGF in the normal subjects or in the patients with AR. In contrast, playing video games enhanced wheal responses induced by HDM and JCP in patients with AEDS. This was not a result of enhanced non-specific irritation of the skin histamine or control solution. Enhancement was allergen-specific, as no wheal responses were induced by latex, to which the patients with AEDS were not sensitized. Enhancement of wheal responses was still significant ($P < 0.01$) after 2 h (10.1 ± 0.5 mm by HDM and 9.8 ± 0.4 mm by JCP), but not after 4 h (9.1 ± 0.4 mm by HDM and 7.9 ± 0.4 mm by JCP). Plasma levels of SP, VIP and NGF were elevated by playing video games in the patients with AEDS. In another experiments, the effects of oxatomide (60 mg day⁻¹) on enhancement of plasma SP, VIP and NGF in the patients with AEDS ($n = 9$) were studied. Patients took oxatomide, and then played the video game. Oxatomide did not prevent

Table 1 Effect of playing video games on skin wheal responses and plasma variables

	Normal		AR		AEDS	
	Before	After	Before	After	Before	After
Skin wheal (mm)						
HDM	0.0 (0.0)	0.0 (0.0)	8.2 (0.4)	8.4 (0.3)	8.4 (0.3)	12.6 (0.5)*
JCP	0.0 (0.0)	0.0 (0.0)	7.7 (0.3)	7.9 (0.3)	7.4 (0.3)	11.5 (0.5)*
Latex	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Histamine	6.0 (0.2)	5.8 (0.2)	6.3 (0.2)	6.4 (0.2)	6.1 (0.2)	6.2 (0.2)
Control solution	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Plasma (pg mL ⁻¹)						
SP	43.4 (1.9)	41.9 (1.7)	55.2 (1.7)	58.4 (1.6)	79.3 (2.8)	132.4 (3.8)*
VIP	11.7 (0.5)	12.3 (0.6)	18.5 (0.9)	18.9 (0.9)	22.4 (0.9)	34.7 (1.1)*
NGF	129 (7)	120 (6)	612 (6)	629 (7)	1879 (79)	2893 (93)*

Effects of playing video games on skin wheal responses by house dust mite (HDM), Japanese cedar pollen (JCP), latex, histamine and control was studied in normal subjects (normal), patients with allergic rhinitis (AR) and patients with atopic eczema/dermatitis syndrome (AEDS).

Simultaneously, plasma levels of substance P (SP), vasoactive intestinal peptide (VIP) and nerve growth factor (NGF) were measured. Values are the mean (SEM).

*Significant enhancement ($P < 0.001$).

Table 2 Effect of playing video games on *in vitro* production of IgE and cytokines

	<i>In vitro</i> production (ng mL ⁻¹)					
	Normal		AR		AEDS	
	Before	After	Before	After	Before	After
Total IgE	< 0.3	< 0.3	12.5 (0.5)	12.7 (0.6)	13.5 (0.6)	21.7 (0.7)*
Anti-HDM IgE	< 0.3	< 0.3	3.5 (0.2)	3.7 (0.2)	3.3 (0.2)	5.7 (0.3)*
IL-4	43 (2)	39 (2)	313 (12)	320 (15)	459 (14)	738 (25)*
IL-10	13 (1)	11 (1)	102 (7)	110 (7)	118 (7)	195 (10)*
IL-13	31 (2)	33 (2)	224 (10)	136 (10)	289 (10)	491 (15)*
IFN- γ	42 (3)	40 (3)	105 (4)	100 (2)	118 (4)	67 (3) [†]
IL-12	14 (1)	15 (1)	82 (2)	85 (2)	89 (3)	52 (2) [†]

See legend for Table 1.

Values are mean (SEM).

*Significant enhancement ($P < 0.001$).

[†]Significant reduction ($P < 0.001$).

HDM, house dust mite; AEDS, atopic eczema/dermatitis syndrome.

enhancement of plasma parameters caused by playing video games: plasma levels of SP, VIP and NGF (pg mL⁻¹, mean $\pm$ SEM) were 83.4 ± 2.5 , 25.3 ± 1.2 and 1993 ± 85 before playing video games and 130.9 ± 3.2 , 36.7 ± 1.3 and 2925 ± 97 after playing video games.

As shown in Table 2, playing video games did not modulate *in vitro* production of IgE or cytokines (IL-4, IL-10, IL-12, IL-13 and IFN- γ) in the normal subjects or in the patients with AR. However, playing video games enhanced *in vitro* production of total IgE and anti-HDM IgE with concomitant increased production of IL-4, IL-10 and IL-13 and decreased production of IFN- γ and IL-12 in the patients with AEDS. To test the psychological effect of the skin test and blood draw, a control group (the same 25 patients with AEDS) were tested at a 2-h interval without playing video games. Neither skin wheal responses (mm, mean $\pm$ SEM) induced by HDM (8.5 ± 0.3 vs. 8.2 ± 0.3)

or by JCP (7.1 ± 0.3 vs. 7.3 ± 0.3) nor plasma levels (pg mL⁻¹) of SP (73 ± 3 vs. 75 ± 3), VIP (20 ± 1 vs. 18 ± 1) or NGF (1814 ± 74 vs. 1832 ± 80) were changed. *In vitro* production (ng mL⁻¹) of IL-4 (421 ± 16 vs. 405 ± 15), IL-10 (102 ± 8 vs. 108 ± 9), IL-13 (234 ± 10 vs. 215 ± 11), IFN- γ (93 ± 5 vs. 98 ± 6) or IL-12 (81 ± 3 vs. 87 ± 4) were also unchanged. These results implied playing video games significantly elevated systolic blood pressure (mmHg, mean $\pm$ SEM) in the patients with AEDS (109 ± 4 vs. 131 ± 5) ($P \leq 0.001$), but not in the normal subjects (112 ± 4 vs. 110 ± 4) or the patients with AR (107 ± 4 vs. 111 ± 4). In addition playing video games significantly increased heart rate (b.p.m.) in the patients with AEDS (68.7 ± 1.4 vs. 80.2 ± 1.8) ($P \leq 0.001$), but not in the normal subjects (69.7 ± 1.5 vs. 70.3 ± 1.7) or the patients with AR (68.9 ± 1.5 vs. 69.8 ± 1.6).

As shown in Table 3, the wheal responses induced by HDM and JCP in the mobile phone study were significantly

Table 3 Effect of frequently ringing mobiles phones on skin wheal responses and plasma variables

	Normal		AR		AEDS	
	Before	After	Before	After	Before	After
Skin wheal (mm)						
HDM	0.0 (0.0)	0.0 (0.0)	7.3 (0.4)	7.6 (0.4)	7.1 (0.4)	9.6 (0.5)*
JCP	0.0 (0.0)	0.0 (0.0)	9.4 (0.5)	9.2 (0.5)	9.1 (0.4)	11.8 (0.5)*
Latex	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Histamine	5.8 (0.2)	5.6 (0.2)	6.1 (0.3)	6.2 (0.3)	6.4 (0.3)	6.2 (0.3)
Control solution	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Plasma (pg mL ⁻¹)						
SP	42.2 (1.7)	40.2 (1.6)	63.8 (2.5)	65.2 (2.8)	85.3 (3.9)	117.4 (4.5)*
VIP	12.1 (0.6)	11.3 (0.5)	17.7 (0.8)	18.5 (0.9)	21.7 (0.8)	32.5 (1.0)*
NGF	122 (6)	110 (5)	284 (11)	267 (10)	873 (42)	1133 (51)*

Subjects received 30 incidences of ringing mobile phones, and skin wheal responses and plasma levels of SP, VIP and NGF were measured. Values are mean (SEM).

*Significant enhancement ($P < 0.001$).

HDM, house dust mite; JCP, Japanese cedar pollen; SP, substance P; VIP, vasoactive intestinal peptide; NGF, nerve growth factor; AEDS, atopic eczema/dermatitis syndrome.

enhanced in the patients with AEDS, but not in the normal subjects or the patients with AR. Again, this was allergen-specific, as wheal responses by latex, histamine or control solution were not enhanced. Plasma levels of SP, VIP and NGF were elevated by the ringing in the patients with AEDS, but not in the normal subjects or the patients with AR. The different NGF levels in Tables 1 and 3 resulted from the severity of the diseases, as previously reported [14,15]. Exposure to frequently ringing mobiles phones significantly elevated systolic blood pressure (mmHg, mean $\pm$ SEM) in the patients with AEDS (111 ± 4 vs. 138 ± 5) ($P \leq 0.001$), but not in the normal subjects (108 ± 4 vs. 111 ± 4) or the patients with AR (110 ± 4 vs. 114 ± 5). Frequent exposure to the ringing of mobile phones significantly increased heart rate (b.p.m.) in the patients with AEDS (68.1 ± 1.3 vs. 82.4 ± 1.9) ($P \leq 0.001$), but not in the normal subjects (69.6 ± 1.7 vs. 70.2 ± 1.8) or the patients with AR (68.5 ± 1.6 vs. 69.3 ± 1.7).

Again, taking oxatomide (60 mg) did not prevent the elevation of plasma parameters by exposure to ringing. The effect of exposure to ringing was studied in six patients with AEDS who took oxatomide. Plasma levels of SP, VIP and NGF (pg mL⁻¹, mean $\pm$ SEM) were 81.2 ± 2.3 , 20.9 ± 1.4 and 825 ± 50 , respectively, before exposure to the ringing mobile phones and 1252.0 ± 4.0 , 35.6 ± 1.3 and 1328 ± 67 , respectively, after exposure.

Discussion

Atopic eczema/dermatitis syndrome is often exacerbated by stress. The enhanced allergen-induced, but not histamine-induced, skin wheal responses suggest that playing video games and exposure to frequently ringing mobiles phones may be stressful to patients with AEDS, as indicated by the enhanced IgE-mediated release of histamine. This may be a result of enhanced release of SP, VIP and NGF, as playing

video games and exposure to frequently ringing mobiles phones increased plasma levels of SP, VIP and NGF, which have been reported to induce mast cell degranulation [9–11]. In addition, playing video games enhanced *in vitro* allergen-induced IgE production in the patients with AEDS, which agrees with the report that stress enhances serum IgE levels in patients with AEDS [5]. It has been reported that stress down-regulates Th1 cytokine (IFN- γ and IL-2) and up-regulates Th2 cytokine (IL-4, IL-5, and IL-6) production [6]. In addition, the author has shown that playing video games down-regulates Th1 cytokine (IFN- γ and IL-12) and up-regulates Th2 cytokine (IL-4, IL-10 and IL-13) production. Collectively, playing video games skewed the cytokine pattern toward Th2 type, which in turn enhanced production of total IgE and anti-HDM IgE in the patients with AEDS. These results indicate that although playing video games may be amusing, it enhances allergic responses in patients with AEDS. This effect was not confined to aggressive video games. Similar results were observed while the patients played non-aggressive video games, including SUPER MARIO KART and Perfect Eleven (data not shown).

In contrast to the patients with AEDS, playing video games or exposure to frequently ringing mobiles phones had no effect on the normal subjects or the patients with AR. The author also studied the effect of playing video games or exposure to frequently ringing mobile phones on patients with bronchial asthma ($n = 20$). Playing video games failed to induce wheal response (mm, mean $\pm$ SEM) by HDM (8.9 ± 0.5 at baseline vs. 8.5 ± 0.0 after playing video games) or JCP (5.4 ± 0.3 at baseline vs. 5.6 ± 0.3 after playing video games). The frequently ringing mobile phones also had no effect on wheal responses induced by HDM (8.6 ± 0.5 vs. 8.8 ± 0.5) or by Japanese cedar pollen dust (5.2 ± 0.3 vs. 5.0 ± 0.3) in patients with bronchial asthma. Thus, aggravation of allergic responses by playing video games or exposure to frequent ring of mobile phones may be specific to patients with AEDS. This is important in the treatment of patients with AEDS, as stress in daily life aggravates

symptoms in AEDS. Although the experimental condition of exposure to frequent ringing may not be similar to the situation in daily life, exposure to incessant ringing of mobile phones is not unusual when travelling by train in Japan. In another study, writing mail on mobile telephones for 2 h enhances allergen-induced skin wheal responses and increases plasma levels of SP, VIP and NGF in patients with AEDS, but not in normal subjects, patients with AR or bronchial asthma (manuscript in preparation).

The pathogenesis and aggravating factors for AEDS are multiple, including IgE-mediated allergic responses, delayed immune responses, and environmental and psychological factors. Stress aggravates AEDS, while AR is a IgE-mediated allergic response and usually is not stress related [5,22]. This difference may be one of the reasons for the different responses to stress by playing video games and exposure to frequently ringing mobiles phones between AEDS patients and AR patients.

These results indicate that high technology in modern world may be stressful to patients with AEDS, and it may play a role in aggravating allergic symptoms. A study is currently in progress to alleviate technology-related stress.

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