

Listening to Mozart Reduces Allergic Skin Wheal Responses and In Vitro Allergen-specific IgE Production in Atopic Dermatitis Patients With Latex Allergy

Hajime Kimata, MD, PhD

In atopic dermatitis patients with latex allergy, listening to Mozart reduced skin wheal responses induced by latex, but not by histamine, whereas listening to Beethoven failed to produce similar results. Listening to Mozart also decreased in vitro total IgE and latex-specific IgE production with concomitant skewing of the cytokine pattern toward the Th1 type, that is, an increase in Th1 cytokine production and decrease in Th2 cytokine production by peripheral blood mononuclear cells, whereas listening to Beethoven failed to do so. These results suggest that therapy using specific types of music may be an effective treatment of allergic diseases.

Index Terms: atopic dermatitis, latex allergy, latex-specific IgE, listening to Mozart, skin wheal response

INTRODUCTION

Music therapy has been reported to modulate immunological and physiological responses. Music therapy (1) decreased peripheral blood cell count of lymphocytes and neutrophils, (2) increased salivary secretory IgA, (3) decreased plasma beta-endorphin and cortisol, and (4) counteracted the increase in heart rate and blood pressure during treadmill running in normal subjects.¹⁻⁵ In addition, listening to Mozart was reported to enhance spatial-temporal reasoning and increase perception of relaxation in normal subjects. This was specific to Mozart, because listening to Beethoven had no effect.^{6,7} On the other hand, music therapy decreased asthma symptoms in patients with bronchial asthma.⁸ However, the effect of music therapy on allergic responses in allergic diseases such as atopic dermatitis (AD) was not reported.

Dr Kimata is with the Department of Allergy at Ujitakeda Hospital, Kyoto, Japan.

Stress responses in patients with AD were altered, and these patients were vulnerable to stress.⁹ I previously reported that stress by microwave radiation or computer use enhanced allergic responses in AD patients.^{10,11} Moreover, in atopic patients, stress caused down-regulation of Th1 and a selective up-regulation of Th2 type cytokines, which resulted in enhancement of IgE production and aggravation of allergic symptoms.¹² In contrast, relaxation caused by laughter reduced allergen-induced skin wheal responses in AD patients.¹³ Therefore, it would be intriguing to hypothesize that relaxation by listening to Mozart or Beethoven could reduce allergic responses in AD patients with concomitant skewing of cytokine patterns toward the Th1 type, for instance, an increase in Th1 cytokine production and decrease in Th2 cytokine production. I previously reported that in vitro latex-specific IgE production can be induced in AD patients with latex allergy.¹⁴ Using this system, I studied the effect of listening to Mozart or Beethoven on latex-induced skin wheal responses and in vitro production of latex-specific IgE and cytokines in AD patients with latex allergies.

METHODS

After obtaining informed consent, I studied 50 AD patients with latex allergies. All of the patients had moderate AD according to the SCORAD index¹⁵ and were allergic to latex as determined by clinical symptoms to latex, positive skin prick test to latex, and positive serum latex-specific IgE.¹⁴ They were treated with the oral anti-allergy medication oxatomide (60 mg) and skin care included washing with povidone iodine and applying nonsteroidal ointment (azulene).¹¹ Subjects did not take oxatomide for 72 hours prior to the study, and they stopped the application of azulene 24 hours prior to the study. I randomly divided the subjects into two groups. There was no difference of age, sex, severity of AD as assessed by SCORAD index, stress levels as assessed by a one-item overall stress rating scale,^{11,12} serum total and latex-specific IgE, or initial levels of allergic responses between the two groups (Table 1). In addition, none of them was familiar with Beethoven or Mozart. This was a double-blinded study. Neither AD patients nor experimenters were aware of the hypothesis. The first group (25 patients) sat on chairs and listened to Beethoven (Symphony No. 6 Op. 68 *Pastoral* 1st mov.: *Allegro ma non troppo*, "Für Elise," and Symphony No. 5 Op. 67 2nd mov.: *Andante con moto*) through speakers of a stereo in a small room for about 30 minutes without engaging in any other activities. One experimenter, who was blinded to the study, operated the stereo. The second group (25 patients) listened to Mozart (Piano Sonata No. 11 K. 331, and Piano Concerto No. 21 K. 567 2nd mov.) through speakers of a stereo in a small room for about 30 minutes without engaging any other activities as above. Another experimenter, who was blinded to the study, operated the stereo for this group.

Before and after the study, the experimenters performed skin prick tests using latex allergen, histamine (10 mg/ml), and a control solution, and after 15 minutes other experimenters who were blinded to the study determined the wheal responses.¹³ In addition, the subjects' stress levels were measured with a one-item overall stress-rating scale.^{11,12} For the one-item rating scale, subjects were asked to rate their overall levels of stress on a scale between 0 (no stress) and 10 (extremely stressed).^{11,12} Simultaneously, experimenters obtained peripheral blood mononuclear cells and cultured them ($2 \times 10^5/0.2$ ml/well) with IL-4 (1000 U/ml), IL-10 (100 ng/ml), anti-CD40 mAb (BL-C4, 100 ng/ml), and latex allergen (0.1 ng/ml) for 14 days. The total IgE and latex-specific IgE production was measured as previously reported by experimenters who were blinded to the study.^{11,14} Experimenters who were blinded to the study also cultured mononuclear cells ($2 \times 10^5/0.2$ ml/well) with latex allergen (0.1 ng/ml) for 5 days, and measured production of IL-4, IL-10, IL-12, IL-13 and IFN- γ by using ELISA (R&D Systems, Inc. Minneapolis, MN). The culture medium was DME, supplemented with Ham's nutrient (DME/F-12) (Sigma Chemical Co., St. Louis, MO), 0.5% BSA, and 50 μ g transferrine.¹⁶ I performed the statistical analysis with Student's *t* test. The ethical committee of our hospital approved this study.

RESULTS

The one-item rating scale was not significantly changed by listening to Beethoven (4.3 ± 0.4 before listening vs 4.1 ± 0.4 after listening), but it was significantly ($p < .001$) reduced by listening to Mozart (4.5 ± 0.4 before listening vs 2.6 ± 0.3 after listening). These results indicate that listening

TABLE 1. Characteristics of the Patients With Atopic Dermatitis and Latex Allergy

Characteristic	First group (Listening to Beethoven)	Second group (Listening to Mozart)
Age (yr)†	32 (21–45)	31 (20–43)
Sex	13 women, 12 men	13 women, 12 men
Severity (SCORAD index)†	28 (18–37)	29 (17–38)
1-item rating scale†	4.3 (2.5–6.1)	4.5 (2.7–6.3)
Duration of atopic dermatitis (yr)†	15 (2–37)	17 (3–40)
Duration of latex allergy (yr)†	11 (3–25)	12 (2–28)
Serum total IgE (IU/ml)†	3683 (1472–6379)	3849 (1392–7256)
Serum latex-specific IgE (UA/ml)†	36 (15–100)	42 (17–100)

†Values are the means (range).

TABLE 2. Effect of Listening to Music on Skin Wheal Responses and In Vitro IgE Production

Variable	Beethoven		Mozart	
	Before	After	Before	After
Skin wheal responses (mm)				
Latex	11.3 ± 0.4	11.9 ± 0.5	12.1 ± 0.5	7.7 ± 0.3*
Histamine	6.9 ± 0.3	7.2 ± 0.3	6.7 ± 0.3	7.0 ± 0.3
Control solution	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
In vitro IgE production (ng/ml)				
Total IgE	41.5 ± 2.3	39.7 ± 2.1	42.4 ± 2.4	27.5 ± 1.4*
Latex-specific IgE	6.5 ± 0.4	6.8 ± 0.5	6.9 ± 0.5	3.0 ± 0.1*

Note. Values are the means ± SEM.

*Significant reduction ($p < .001$) compared to before.

TABLE 3. Effect of Listening to Music on In Vitro Cytokine Production

Cytokine (pg/ml)	Beethoven		Mozart	
	Before	After	Before	After
IL-4	447 ± 12	464 ± 13	429 ± 12	254 ± 8*
IL-13	362 ± 10	356 ± 9	376 ± 9	228 ± 6*
IL-10	137 ± 4	145 ± 5	132 ± 4	95 ± 3*
IFN- γ	119 ± 5	129 ± 6	123 ± 6	220 ± 7**
IL-12	237 ± 6	254 ± 8	242 ± 8	353 ± 9**

Note. Values are the means ± SEM.

*Significant decrease ($p < .001$) compared to before.

**Significant increase ($p < .001$) compared to before.

to Mozart reduced stress in AD patients, whereas listening to Beethoven failed to do so.

As shown in Table 2, the skin wheal responses induced by latex or histamine were not changed after listening to Beethoven. In contrast, the wheal responses induced by latex, but not by histamine, were significantly reduced after listening to Mozart. Moreover, whereas listening to Beethoven had no effect on in vitro production of total IgE and latex-specific IgE by mononuclear cells, listening to Mozart significantly reduced in vitro production of total IgE and latex-specific IgE. The effect of listening to music on in vitro production of cytokines by mononuclear cells was then studied. As shown in Table 3, listening to Beethoven had no effect on production of cytokines by mononuclear cells. In contrast, listening to Mozart decreased production of IL-4, IL-10, and IL-13, while it increased production of IFN- γ and IL-12.

COMMENT

These results demonstrate that listening to Mozart reduced allergen-induced skin wheal responses with a concomitant decrease of total and allergen-specific IgE production. The reduction of wheal response was allergen-specific because listening to Mozart had no effect on histamine-induced wheal responses, that were not allergen-specific. Analysis of production of cytokines indicated that listening to Mozart decreased production of Th2-type cytokines (IL-4, IL-10, IL-13) and increased Th1-type cytokines (IFN- γ , IL-12), which was compatible with the reduction of IgE production.¹⁶

The exact mechanisms of the effect of Mozart are currently under investigation. However, in another study, 15 patients out of a second group listened to Schubert (String Quartet *Rosamunde* 2nd mov., Piano Quintet *Trout* 4th mov., and Symphony No. 8 *Unfinished* 2nd mov.) for about 30 minutes, while 14 patients out of first group listened to

the same Mozart music. Experiments studied the subjects before and after listening for latex-induced skin wheal responses and in vitro latex-specific IgE production by mononuclear cells. The latex-induced wheal responses (mean $\pm$ SEM) were not significantly different before (11.5 ± 0.6 mm) or after (11.8 ± 0.6 mm) listening to Schubert. In addition, in vitro latex-specific IgE production was not significantly different before (5.9 ± 0.6 ng/ml) or after (5.7 ± 0.6 ng/ml) listening to Schubert. Moreover, the one-item rating scale was not significantly different before (4.6 ± 0.4) or after (4.2 ± 0.4) listening to Schubert. In contrast, the latex-induced wheal responses were reduced from 12.2 ± 0.7 mm before to 8.3 ± 0.5 mm after ($p < .01$), and in vitro latex-specific IgE production was reduced from 5.3 ± 0.5 ng/ml before to 2.5 ± 0.2 ng/ml after ($p < .01$) listening to Mozart. In addition, the one-item rating scale was significantly ($p < .01$) reduced from 4.9 ± 0.5 before to 2.9 ± 0.3 after listening to Mozart. Collectively, these results suggest that listening to Mozart reduced stress in both groups of AD patients, whereas listening to Schubert failed to do so. I have also studied the effect of other classical music. Listening to Hayden (Trumpet Concerto in E-flat major 1st mov: Allegro, Symphony No. 101 in D major *The Clock*, 1st mov: Adagio-Presto, 2nd mov: Andante, 3rd mov: *Menuetto*; Allegretto, and 4th mov: *Finale*; Vivace) or Brahms (Clarinet Quintet in B minor 1st mov., Symphony No. 2 in D major 3rd mov., Symphony No. 1 in C minor 3rd mov., and Symphony No. 3 in F major 3rd mov.) failed to reduce allergic skin wheal responses (data not shown).

Thus, the reducing effect on allergic responses may be specific to Mozart. It has been reported that listening to Mozart, but not listening to Beethoven, enhanced spatial-temporal reasoning and increased perception of relaxation.^{6,7} It would be interesting to study whether other classical music, including Schubert, Hayden, or Brahms, could enhance spatial-temporal reasoning and increase perception of relaxations. Detailed analysis is currently in progress. In addition, stress skews the cytokine pattern toward Th1 type in atopic patients.¹² Therefore, it would be intriguing to speculate that increased relaxation induced by listening to Mozart may alleviate allergic responses with concomitant skewing cytokine pattern toward Th1 type, that is, an increase in Th1 cytokine production and decrease in Th2 cytokine production, while listening to other music fails to do so because of less relaxation. This possibility is currently under investigation. It should be pointed out that the "relaxation procedure" used by Wolpe reduced stress.¹⁷ It is possible that such relaxation may also reduce allergic responses and thus may be useful in the treatment of allergic diseases. In fact, I have recently found that inhalation of

valerian oil induced relaxation and reduced allergic skin wheal responses, whereas inhalation of jasmine oil neither induced relaxation nor reduced allergic skin wheal responses. Inhalation of valerian oil reduces latex allergen-induced skin wheal responses and in vitro latex-specific IgE and IgG4 production in patients with latex allergy (Kimata H, in press).

Music therapy modulates various immunological and physiological responses depending on the subjects. Music therapy induces: (1) an increase in salivary secretory IgA in healthy adults, (2) an increase in natural killer cytotoxicity in healthy adults, (3) a decrease in mood disturbance and plasma cortisol levels in healthy adults, (4) a reduction of depression in older adults, (5) a relative right frontal activation in depressed adolescents, (6) the alleviation of symptoms in patients with Parkinson's disease, (7) a reduction of anxiety in children with cancer, and (8) the alleviation of pain in adult patients with advanced cancer.^{2,3,4,18,19,20,21} Our results demonstrate for the first time that music therapy reduces allergic response with a skewing cytokine pattern toward the Th1 type. Music therapy could have various beneficial effects, depending on diseases. This is not surprising because there is precedence. It has been reported that laughter has various beneficial effects depending on the subjects. It induces: (1) an increase in natural killer cytotoxicity in healthy adults, (2) the alleviation of pain in patients with ankylosing spondylitis, (3) a reduction of plasma levels of interleukin 6 in patients with rheumatoid arthritis, and (4) a reduction of allergic responses in AD patients.^{13,22,23,24}

These results may have implications for the neuro-immunological mechanisms of music therapy. Listening to specifically appropriate music may be useful in the treatment of allergic diseases.

REFERENCES

1. Rider MS, Achterberg J. Effect of music-assisted imagery on neutrophils and lymphocytes. *Biofeedback Self Regul.* 1989;14:247-257.
2. Rider MS, Achterberg J, Lawlis GF, Goven A, Toledo R, Butler JR. Effect of immune system imagery on secretory IgA. *Biofeedback Self Regul.* 1990;15:317-333.
3. McKinney CH, Tims FC, Kumar AM, Kumar M. The effect of selected classical music and spontaneous imagery on plasma beta-endorphin. *J Behav Med.* 1997;20:85-99.
4. McKinney CH, Antoni MH, Kumar M, Tims FC, McCabe PM. Effects of guided imagery and music (GIM) therapy on mood and cortisol in healthy adults. *Health Psychol.* 1997;16:390-400.
5. Szmedra L, Bacharach DW. Effect of music on perceived exertion, plasma lactate, norepinephrine and cardiovascular hemo-

- dynamics during treadmill running. *Int J Sports Med*. 1998;19:32–37.
6. Rauscher FH, Shaw GL, Ky KN. Music and spatial task performance. *Nature*. 1993;365:611.
 7. Bodner M, Muftuler LT, Nalcioglu O, Shaw GL. fMRI study relevant to the Mozart effect: brain areas involved in spatial-temporal reasoning. *Neurol Res*. 2001;23:683–690.
 8. Lehrer PM, Hochron SM, Mayne T, et al. Relaxation and music therapies for asthma among patients prestabilized on asthma medication. *J Behav Med*. 1994;17:1–24.
 9. Buske-Kirschbaum A, Geiben A, Hollig H, Morschhauser E, Hellhammer D. Altered responsiveness of the hypothalamus-pituitary-adrenal axis and the sympathetic adrenomedullary system to stress in patients with atopic dermatitis. *J Clin Endocrinol Metab*. 2002;87:4245–4251.
 10. Kimata H. Enhancement of allergic skin wheal responses by microwave radiation from mobile phones in patients with atopic eczema/dermatitis syndrome. *Int Arch Allergy Immunol*. 2002;129:348–360.
 11. Kimata H. Enhancement of allergic skin wheal responses and in vitro allergen-specific IgE production by computer-induced stress in patients with atopic dermatitis. *Brain Behav Immun*. 2003;17:134–8.
 12. Kang D-H, Fox C. Th1 and Th2 cytokine response to academic stress. *Res Nurs Health*. 2001;24:245–257.
 13. Kimata H. Effect of humor on allergen-induced wheal reactions. *JAMA*. 2001;285:738.
 14. Kimata H. In vitro induction of IgE antibody to latex. *Allergy*. 2001;56:914.
 15. Kunz B, Oranje AP, Labreze L, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European task force on atopic dermatitis. *Dermatology*. 1997;195:10–19.
 16. Kimata H, Fujimoto M, Ishioka C, Yoshida A. Histamine selectively enhances human immunoglobulin E (IgE) and IgG4 production induced by anti-CD58 monoclonal antibody. *J Exp Med*. 1996;184:357–364.
 17. Wolpe J. Deconditioning and ad hoc uses of relaxation: an overview. *J Behav Ther Exp Psychiatry*. 1984;15:299–304.
 18. Hasegawa T, Kubota N, Inagaki T, Shinagawa N. Music therapy induced alterations in natural killer cell count and function. *Jpn J Geriatr*. 2001;38:201–204. (In Japanese)
 19. Field T, Martinez A, Nawrocki T, Pickens J, Fox NA, Schanberg S. *Adolescence*. 1998;33:109–116.
 20. Hanser SB, Thompson LW. Effects of a music therapy strategy on depressed older adults. *J Gerontol*. 1994;49:265–269.
 21. Pacchetti C, Aglieri R, Mancini F, Martigoni E, Nappi G. Active music therapy and Parkinson's disease: methods. *Funct Neurol*. 1998;13:57–67.
 22. Berk LS. Eustress of mirthful laughter modifies natural killer activity. *Clin Res*. 1989;37:115A.
 23. Cousins N. Anatomy of an illness (as perceived by the patients). *N Eng J Med*. 1976;295:1458–1463.
 24. Yoshino S, Fujimori J, Kohda M. Effects of mirthful laughter on neuroendocrine and immune system in patients with rheumatoid arthritis. *J Rheumatol*. 1996;23:793–794.