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ORIGINAL ARTICLE

Association between perceived happiness levels and peripheral circulating pro-inflammatory cytokine levels in middle-aged adults in Japan

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Abstract

OBJECTIVES: The idea that perceived happiness may be associated with health and well-being is a recent topic of focus. However, the neurobiological mechanisms underlying the positive effects of happiness on psychological and physiological wellness remain obscure. In this study, we attempted to clarify the association between systemic inflammation and happiness.
METHODS: We recruited 160 healthy volunteers for experiment 1 and compared peripheral inflammatory markers, namely the concentrations of pro-inflammatory cytokines in the serum, between perceived high-happiness and low-happiness groups. Subsequently, we recruited 7 romantic couples for experiment 2 and investigated changes in peripheral pro-inflammatory cytokine levels after the evocation of happiness, which was induced by warm physical contact with the partner.
RESULTS: We found that circulating levels of interferon-γ (IFN-γ), which can affect brain functions and induce depressive symptoms, were lower in the high-happiness group than in the low-happiness group. A negative correlation between the levels of perceived happiness and IFN-γ concentrations was also observed. Furthermore, we also found that experimentally induced happiness could reduce peripheral IFN-γ levels.
CONCLUSIONS: These results revealed an association between the perception of happiness and systemic inflammation. Increased happiness may suppress the peripheral circulation of pro-inflammatory cytokines.

INTRODUCTION

It is well known that stress and anxiety can lead to depression (Magalhaes *et al.* 2010). One of the biological explanations why such psychosocial stressors induce depression is the mediation of pro-inflammatory cytokines, the immune signaling molecules that promote systemic inflammation, such as tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) (Maes *et al.* 2011). The central nervous and immune systems are interrelated via complex biochemical pathways (Ader, 2000), and psychoneuroimmunologic studies have demonstrated that such psychosocial stressors can induce the active secretion of pro-inflammatory cytokines from immune cells stimulated by the sympathetic nervous system. Peripheral circulating pro-inflammatory cytokines can reach the brain via leaky regions in the blood-brain barrier, active transport molecules, and afferent nerve fibers (Raison *et al.* 2006; Dantzer *et al.* 2008). The enzyme indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan along the kynurenine pathway, is expressed in all organs including the brain, and the enzymatic activity of IDO can be potently activated by a number of cytokines, including TNF-α and IFN-γ. Activation of IDO results in decreased levels of tryptophan and other tryptophan-derived metabolites, such as 5-hydroxytryptamine (serotonin). Serotonin in the brain has an antidepressant effect; therefore, the deceleration of serotonin in the brain by pro-inflammatory cytokines may induce depression. In fact, previous studies indicated that circulating pro-inflammatory cytokine levels in individuals with depressive symptoms were higher than those in individuals with no depressive symptoms (Pan *et al.* 2008).

The idea that perceived happiness may be associated with health and well-being has recently been investigated intensely. Individuals with high levels of perceived happiness have reduced sympathetic activation after exposure to psychological stressors compared to those with low levels of perceived happiness (Horiuchi *et al.* 2008). A recent study indicated that the level of perceived happiness is negatively correlated with depression and anxiety (Shimai *et al.* 2004). The biological mechanism underlying the positive effect of happiness remains obscure; however, it is suggested that circulating pro-inflammatory cytokine levels may be lower in individuals with high-perceived happiness than in individuals with low-perceived happiness, although this has yet to be demonstrated. In addition, it is still unclear whether peripheral circulating pro-inflammatory cytokine levels are decreased if happiness is experimentally evoked. We have recently demonstrated that warm physical contact with the partner can increase subjective happiness (Matsunaga *et al.* 2009a). Accompanying feelings of happiness, serum levels of albumin were also increased (Matsunaga *et al.* 2009a). A previous study demonstrated a negative correlation between peripheral albumin levels and pro-inflammatory cytokine levels (Odamaki *et al.* 2004), suggesting that pro-inflammatory cytokine levels may also be decreased by warm partner contact, accompanied by decrease in albumin levels.

Based on these previous observations, we first compared the serum concentrations of pro-inflammatory cytokines (interleukin-6 (IL-6), TNF-α, and IFN-γ) and health-related quality of life (QOL) between individuals with high-perceived happiness and those with low-perceived happiness (Experiment 1). Subsequently, we investigated whether warm partner contact could decrease the serum concentrations of pro-inflammatory cytokines (IL-6, TNF-α, and IFN-γ) (Experiment 2). Some reports have noted gender-related differences regarding the levels of perceived happiness and physiological reactivity (Shimai *et al.* 2004; Bosch *et al.* 2005). Further, obesity is strongly associated with circulating pro-inflammatory cytokine levels, as adipose tissue is a major production site of inflammatory markers (Hamer & Stamatakis 2008). Thus, we compared the levels of inflammatory markers by using age-, gender-, and BMI-matched groups.

METHODS

Experiment 1

Participants

We recruited 160 healthy volunteers (77 males and 83 females; age range: 19–40 years) for experiment 1. The participants were Japanese undergraduate and graduate students at Nagoya University and Mie University and technical staff at Aichi Medical University and Fujita Health University. Participants were instructed not to eat 2 h before blood sampling, but they were allowed to consume non-alcoholic and caffeine-free fluids. All participants provided written informed consent in accordance with the Declaration of Helsinki. Participants were excluded if they had any chronic or oral illness, if they had taken medication known to influence immunity such as a steroid during the 3-month period before the experiment, or if they used oral contraceptives. In addition, participants who contracted an infectious illness within 3 weeks before the experiment were rescheduled. This study was approved by the Ethics Committee of Fujita Health University. To screen individuals with higher or lower levels of perceived happiness, we requested that they use the Japanese version of the subjective happiness scale (JSHS) (Shimai *et al.* 2004). The JSHS is a 4-item scale that measures relatively stable perceived happiness. The internal consistency, test-retest reliability, convergent validity, and discriminant validity of the JSHS have been confirmed (Shimai *et al.* 2004). The results of this screening investigation indicated that the mean JSHS score for the participants was 4.83 with a standard deviation (SD) of 0.9, which was similar to that reported previously (Shimai *et al.* 2004). According to the mean JSHS score of the participants, we classified respondents with scores exceeding 5.50 as high-happiness respondents (n = 48) and those with scores below 4.25 as low-happiness respondents (n = 48).

Blood sampling and measurements of cytokine concentrations

Blood sampling was performed between 1400 and 1700 h to minimize the influence of circadian rhythms on cytokines. Furthermore, women were examined during the late luteal and early follicular phases of the menstrual cycle when the secretion of female sex hormones is low, thus minimizing the influences of these hormones on the immune system. Blood samples were collected in serum-separator tubes and centrifuged at $3000 \times g$ for 10 min; the serum was separated and then stored at −80 °C until analysis. The levels of several pro-inflammatory serum cytokines (IL-6, TNF-α, and IFN-γ) were determined by a BD™ Cytometric Bead Array (Human Th1/Th2 Cytokine Kit II; BD Biosciences, San Diego, CA) according to the manufacturer's instructions.

Measurement of health-related QOL

The Japanese-translated version of the Short-Form 36 Health Survey (SF-36) was used to assess the impact of 8 QOL dimensions (physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health) on health-related QOL. This translated version has been studied extensively for its reliability and validity (Fukuhara *et al.* 1998a, b). We displayed the 8 dimension scores with the raw values.

Statistical analyses of self-reported and physiological data

The results are expressed as means ± standard error of the mean (SEM). We compared age, BMI, health-related QOL, and circulating levels of IL-6, TNF-α, and IFN-γ by Student's *t* test between the high-happiness and low-happiness groups. Pearson's correlation coefficient between the levels of perceived happiness and IFN-γ concentrations was computed using the entire sample (n = 160).

Experiment 2

Participants

Fourteen healthy volunteers (7 romantic couples; 7 males and 7 females) participated in experiment 2. Patient ages ranged from 21 to 38 years. All participants provided written informed consent in accordance with the Declaration of Helsinki. The participants received no medication during the experimental period. They were requested to evaluate their feelings of romantic love for their partners by using the passionate love scale (PLS) (Hatfield & Sprecher, 1986) (example items: "Sometimes I can't control my thoughts; they are obsessively focused on _____;" I would rather be with _____ than anyone else"). Four participants were evaluated as "extremely passionate," 7 as "passionate," and 3 as "average"; therefore, all couples may be considered to have relatively passionate love. This study was approved by the Human Studies Committee of Aichi Medical University.

Experimental procedure

Each couple entered an experimental room, following which they were given instructions prior to the commencement of the experiment. The couple was instructed not to eat and drink during the experimental session. In the warm contact condition, participants were first requested to evaluate their present happiness levels, and the first blood sample was obtained. They then freely kissed and hugged their romantic partner, but did not have intercourse, for 1 h in a room with closed doors. After the warm contact session, a second blood sample was obtained, and the present happiness level of each participant was evaluated. To assess the level of physical contact, the participants were requested to subjectively rate the following 3 questions on a scale of 1 (not at all) to 7 (Yes, extremely): Did you kiss and hug your partner very much? (contact); Did you evoke much love? (love); Did you sense your partner's love? (love). The average value of the rating score of contact was 5.64 ± 0.29, and the average value of the rating score of love was 11.28 ± 0.58. Because both values were higher than the neutral values (4 (contact) and 8 (love)), the participants were believed to have engaged in extensive warm partner contact during the warm contact session.

In the control condition, participants were first requested to evaluate their present happiness levels, and the first blood samples were obtained. Then, 1 partner remained in the experimental room, while the other partner was moved to another experimental room. The partners then read a book separately for 1 h in a room with closed doors. The content of the books did not include romance. After the reading session, a second blood sample was obtained from each participant, and his or her present happiness level was evaluated. The order of the 2 conditions was counterbalanced across the couples, and there was at least a 2-week interval between the 2 conditions.

Measurement of happiness feeling

To evaluate the feelings of happiness of the participants, they were asked to subjectively evaluate their present emotions by rating the following question on a scale of 1 (not at all) to 7 (Yes, extremely): Do you feel happy at present? (happiness).

Measurements of cytokine concentrations

Blood samples were collected in serum-separator tubes and centrifuged at $3000 \times g$ for 10 min; the serum was separated and then stored at −80 °C until analysis. Cytokine levels were assessed as described in a previous section.

Statistical analyses of self-reported and physiological data

The results were expressed as mean ± SEM. The psychological and physiological indices were compared using 2-way repeated-measures analysis of variance (ANOVA) [condition (control vs. warm contact) × period (before vs. after)] followed by paired *t* tests.

RESULTS

Experiment 1: *Association between the level of perceived happiness and those of circulating pro-inflammatory cytokines*

As shown in Table 1, there were no significant differences in gender distribution, age, and BMI between the high-happiness and low-happiness groups. Using these gender-, age-, and BMI-matched groups, to assess whether the level of perceived happiness is associated with health-related QOL and the peripheral pro-inflammatory cytokine levels, we compared the scores of the SF-36 subscales and serum concentrations of IL-6, TNF-α, and IFN-γ between the high-happiness and low-happiness groups. Statistical analysis revealed that the SF-36 subscale scores of general health (df=94, t=–3.15, $p<0.01$), vitality (df=94, t=–6.36, $p<0.01$), emotional role (df=94, t=–2.22, $p<0.05$), and mental health (df=94, t=–5.03, $p<0.01$) were significantly higher in the high-happiness group than in the low-happiness group. Interestingly, serum concentrations of IFN-γ were significantly lower in the high-happiness group (df=94, t=–2.12, $p<0.05$) than in the low-happiness group. No significant differences were observed between the IL-6 and TNF-α levels between the 2 groups. In addition, Pearson's correlation coefficient between the level of perceived happiness and IFN-γ concentrations was computed, and a significant negative correlation was observed (r(160)=–0.23, $p<0.01$; Figure 1A).

Tab. 1. Comparisons of gender, age, BMI, SF-36 subscale scores, and serum cytokine concentrations between the high-happiness and low-happiness groups.

	Low (<4.25)	High (> 5.50)
Gender (male female)	25/23	24/24
Age	22.64±0.64	23.46±0.73
BMI	20.81±0.53	20.77±0.43
SF-36 subscales		
Physical functioning	29.39±0.27	29.43±0.14
Physical role	18.83±0.31	18.96±0.39
Bodily pain	3.93±0.25	4.02±0.27
General health	17.42±0.54	19.79±0.49**
Vitality	11.84±0.38	15.05±0.35**
Social functioning	8.67±0.24	9.00±0.17
Emotional role	12.06±0.43	13.33±0.38*
Mental health	17.11±0.52	20.32±0.36**
Cytokines (pgml)		
IL-6	2.63±0.52	1.83±0.23
TNF-α	2.35±0.24	2.23±0.18
IFN-γ	7.58±0.88	5.45±0.47*

Each result represents the mean±SEM concentration or rating score. **$p<0.01$ and *$p<0.05$ vs. low-happiness group by Student's *t* test.

Experiment 2: *Effect of happiness on circulating pro-inflammatory cytokine level*

To assess changes in the levels of happiness and those of peripheral circulating pro-inflammatory cytokine after warm partner contact, the participants were asked

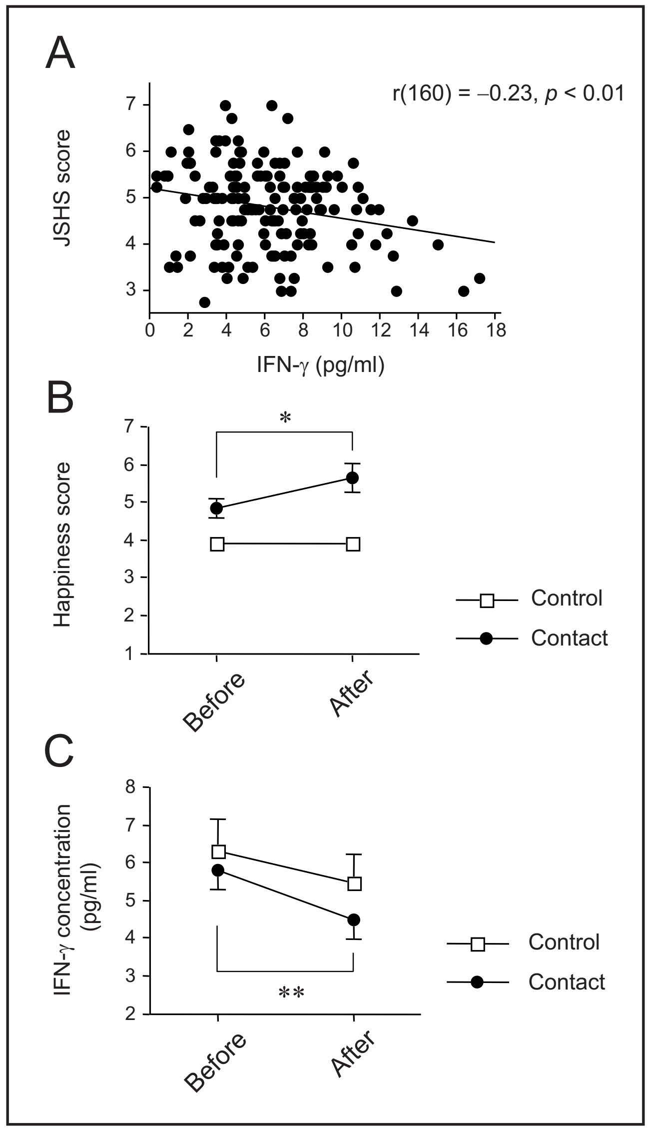

Fig. 1. (A) Scatter plot showing the negative correlation between the level of perceived happiness and serum IFN-γ concentrations (r(160)=–0.23, $p<0.01$). (B) Change in happiness feelings after warm partner contact. *$p<0.05$ vs. before contact by paired *t* test. (C) Changes in serum IFN-γ concentrations after warm partner contact. **$p<0.01$ vs. before contact by paired *t* test.

to rate their present happiness states using a 7-point scale, and blood samples were collected before and after warm partner contact. ANOVA revealed significant interactions between the condition (control or warm contact) and period (before or after) for the rating score of happiness ($F(1,26) = 2.57$, $p < 0.05$, Figure 1B). Further analyses using the paired *t* test revealed that the rating score for happiness increased significantly ($df = 13$, $t = -2.28$, $p < 0.05$) after warm partner contact. Subsequently, we analyzed changes in pro-inflammatory cytokine levels after warm partner contact. Interestingly, ANOVA revealed a significant main effect of the period on the concentration of IFN-γ in the serum ($F(1,26) = 10.37$, $p < 0.01$, Figure 1C). Further analyses using the paired *t* test revealed that the IFN-γ concentration decreased significantly ($df = 13$, $t = 3.21$, $p < 0.01$) after warm partner contact, whereas it did not change in the control condition. No significant differences were observed regarding IL-6 and TNF-α levels (data not shown).

DISCUSSION

We first hypothesized that the level of perceived happiness may be associated with systemic inflammation and negatively correlated with peripheral circulating pro-inflammatory cytokines. As expected, the IFN-γ concentration was lower and health-related QOL was higher in individuals with high-perceived happiness than in individuals with low-perceived happiness. The IFN-γ concentration was negatively correlated with the level of perceived happiness. It is known that the elevation of IFN-γ decreases serotonin levels though the modulation of IDO activity; therefore, serotonin may be abundant in the brains of individuals with high-perceived happiness compared to those with low-perceived happiness. Increased serotonin levels may enhance the reactivity toward positive stimuli. A previous study demonstrated that antidepressant treatment enhances amygdala response to happy faces (Norbury *et al.* 2009). Our previous study also demonstrated that the short form of the serotonin transporter gene-linked polymorphic region, which increases serotonin secretion from presynaptic neurons through reduced serotonin reuptake, also enhances amygdala response to desired persons (Matsunaga *et al.* 2010). When IFN-γ levels decrease, the reactivity to positive stimuli increases, and consequently, the evocation of happiness is enhanced.

We subsequently assessed whether experimentally induced happiness could decrease circulating IFN-γ levels. In this study, we used warm physical contact toward the love partner as the happiness inducer. Interestingly, warm partner contact reduced serum IFN-γ concentrations concurrently with the evocation of happiness. The biological mechanism explaining this phenomenon is still under speculation. Happiness is a positive feeling characterized by contentment, satisfaction, joy, pleasure, or love. Dopamine plays an important role in the expression of positive emotions (Aron *et al.* 2005; Bartels & Zeki 2004; Verhoeff *et al.* 2003). The dopaminergic network within the brain, which projects to the prefrontal cortex and striatum from the midbrain region, is known as the "brain reward system" (Aron *et al.* 2005; Bartels & Zeki 2004), and our previous study demonstrated that the brain reward system is associated with levels of perceived happiness (Matsunaga *et al.* 2011). An interaction between dopamine and IFN-γ was previously observed, and the activation of dopamine receptors by dopamine receptor agonists could suppress the production of IFN-γ in T-lymphocytes, which are known to be major producers of IFN-γ (Huang *et al.* 2010). Therefore, it is possible that experimentally induced happiness decreases IFN-γ production through dopamine-dependent mechanisms.

Previous psychoneuroimmunologic studies revealed an association between other inflammatory markers and positive emotional states. It has been demonstrated that higher positive well-being was associated with lower plasma IL-6 levels (Steptoe *et al.* 2009). In addition to IFN-γ, peripheral IL-6 can also reach the brain via leaky regions in the blood-brain barrier, active transport molecules, and afferent nerve fibers. Recent neuroimaging studies directly revealed that vaccination-induced peripheral IL-6 elevation decreased cognitive function through modulation of the activities of several brain regions, such as the insula and anterior cingulate cortex (Harrison *et al.* 2009). These brain regions are also known to be involved in emotional perception (Matsunaga *et al.* 2009b). We investigated the association between levels of perceived happiness and those of peripheral IL-6 in this study; unfortunately, we did not observe an interaction between these 2 variables. Although we cannot deny the possibility that IFN-γ and IL-6 influence different feelings, one of the reasons why we could not detect an interaction between the levels of perceived happiness and those of other pro-inflammatory cytokines may be the relatively small sample size ($n = 160$). Thus, the generalizability of the current findings should be further tested by using larger samples. Nevertheless, the present study demonstrated that the level of perceived happiness influences the levels of peripheral circulating pro-inflammatory cytokines. These results may expand the scope of clinical literature that addresses the links between positive emotions and immunity.

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Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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