Counter-stress effects of relaxation on proinflammatory and anti-inflammatory cytokines ☆

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A B S T R A C T

The counter-stress effects of relaxation on proinflammatory and anti-inflammatory cytokines were examined. From 36 medical students, 18 were randomly assigned to the relaxation group, and 18 were randomly assigned to the non-relaxation group. Relaxation lasted for four weeks. The levels of stimulated production of IL-6, TNF-α, and IL-10, and blood pressure were measured during the non-examination period (baseline period) and the pre-examination period (stress period). The levels of perceived stress were assessed by the Global Assessment of Recent Stress (GARS) scale, the Stress Response Inventory (SRI) and the Symptom Checklist-90-Revised (SCL-90-R) anxiety subscale. Repeat measure ANOVA revealed that the SRI total score, scores of the SCL-90-R anxiety subscale and diastolic blood pressure were significantly higher during the stress period than during the baseline period regardless of groups. The level of IL-6 production was significantly lower but the level of IL-10 production was significantly higher during the stress period than during the baseline period. Significant reduction in the delta (stress period value minus baseline period value) in the total GARS score, systolic and diastolic blood pressure, the levels of IL-6 and TNF-α production but significant enhancement in the delta in the level of the IL-10 production were found in the relaxation group compared with the non-relaxation group. These results suggest that relaxation is associated with reduction in stress-induced psychological or physiological responses and proinflammatory cytokine alterations but with enhancement in stress-induced anti-inflammatory cytokine alteration. Therefore, relaxation is more likely to have counter-stress effect on proinflammatory cytokines than on anti-inflammatory cytokine.

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1. Introduction

Academic stress, such as an examination period for medical students, has long been used as a model for investigating the interaction between stress and immunity. A number of studies using this model have indicated that examination stress down-regulates the immune functions such as the lymphocyte proliferation, the activity of natural killer (NK) cells, the production of interferon-γ (IFN-γ), salivary immunoglobulin A (IgA), latency of herpes virus or Epstein–Barr virus, interleukin-2 (IL-2) receptor gene expression, and mucosal wound healing (Deinzer and Schuller, 1998; Dobbin et al., 1991; Fawzy, 1995; Glaser et al., 1986, 1987, 1990, 1991; Marchesi et al., 1989; Marucha et al., 1998; Rojas et al., 2002). In contrast, however, immune activation in response to examination stress has been reported in other studies. Salivary immunoglobulin A (IgA) levels were reported to be enhanced in students during an

acute stress of an imminent examination (Bosch et al., 1998). The levels of PHA-stimulated IL-2 production and lymphocyte proliferative responses to PHA were also shown to be significantly higher during an examination period compared to a non-examination period (Kang et al., 1996; Koh, 2001; Koh et al., 2006). Similarly, in another study, students with a reaction to examination stress had a significantly higher number of leukocytes, neutrophils, and monocytes during the examination period than those without a stress reaction (Maes et al., 1999).

Proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α), play a pivotal role in coordinating the body's response to inflammation (Papanicolaou et al., 1998; Vassali, 1992). IL-6 and TNF-α, along with interleukin-1 (IL-1), synergistically control infection by regulating the production of acute-phase proteins and by raising body temperature (Suffredini et al., 1999). In contrast, anti-inflammatory cytokines such as interleukin-10 (IL-10) antagonize Th1-like cell functions, such as interferon-γ (IFN-γ) (Segerstrom and Miller, 2004).

Previous research has suggested that psychological stressors might increase the production rate of proinflammatory cytokines, such as IL-1, IL-6, TNF-α, and IFN-γ. Academic examination-related

stress in students was also found to significantly enhance the stimulated production of proinflammatory cytokines, such as IL-6, TNF-α, and IFN-γ (Maes et al., 1998a, 1998b). In particular, high levels of stress perception during the stressful period are known to be related to an increased production of IFN- γ, TNF-α, and IL-6, but not IL-10 (Maes et al., 1998b). However, a meta-analytic study found that brief stressors, such as academic examinations changed the profile of cytokine production via a decrease in a Th1-type cytokine IFN-γ and increases in the Th2-type cytokines IL-6 and IL-10 (Segerstrom and Miller, 2004).

Some studies have suggested that stress-reducing interventions such as relaxation may enhance immune function (Kiekolt-Glaser and Glaser, 1986). Geriatric patients who received relaxation training reported a decrease in distress symptoms coupled with increased natural killer (NK) cell cytotoxicity and decreased antibody titers to latent herpes simplex virus (Kiecolt-Glaser et al., 1985). It was reported that biofeedback-assisted relaxation training was associated with reductions in tension and anxiety and improvement in phagocytic abilities, such as enhanced neutrophil activation (Peavey et al., 1985). In another study, a single 20-min session of relaxation training resulted in a significant increase in salivary IgA concentrations from the pre-relaxation period to the post-relaxation period, in contrast to a non-relaxation control group (Green and Green, 1987). In addition, a study of the effects of relaxation on immunity in males at high risk for human immunodeficiency virus-1 (HIV-1) infection found significant positive correlations between the frequency of relaxation practice and numbers of T helper cells, T inducer cells, the T helper/T suppressor ratio, and the number of natural killer (NK) cells during the high-stress week of serostatus determination (Baggett et al., 1990). However, it was reported that relaxation and visualization therapy did not

affect lymphocyte proliferation in beast cancer patients undergoing radiotherapy (Nunes et al., 2007).

Despite these interesting results on the interrelationships among stress, relaxation, and immunity, little is known about the ability of stress reduction techniques to modulate proinflammatory and anti-inflammatory cytokines in healthy individuals. In terms of the effects of relaxation-based interventions on stress-induced alterations of immune function, the current study sought to determine the counter-stress effects of relaxation on proinflammatory and anti-inflammatory cytokines in healthy individuals facing pre-examination stress.

2. Methods

2.1. Subjects

Volunteers for this research were recruited from a group of second-year medical students at Yonsei University College of Medicine. The chief of the class was asked to verbally notify students of participant recruitment for this study and also to post a notice on the bulletin board. A week later, we explained the design of the study to all students who were willing to take part in the study. Each of them was told they would be paid about 20 dollars for participation in this study. Informed consent was obtained from all participants.

Subjects were all non-smokers. Subjects were excluded if they had taken any medication that might impair immunity (e.g., antibiotics, anti-histamines, corticosteroids, herbal medicines, or psychotropics) within the two weeks prior to testing. An additional criterion for exclusion included any physical diseases (e.g., infectious, allergic, immune, or metabolic diseases such as the common

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                    ┌─────────────────────────┐
                    │ Participant Recruitment │
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          ┌──────────────────────────────────────────────┐
          │ Screened by Self-assessment Questionnaire (n=55) │
          └──────────────────────────────────────────────┘
                                 │  Not meeting inclusion criteria (n=13)
              ┌──────────────────────────────────┐
              │ Eligible for Randomization (n=42) │
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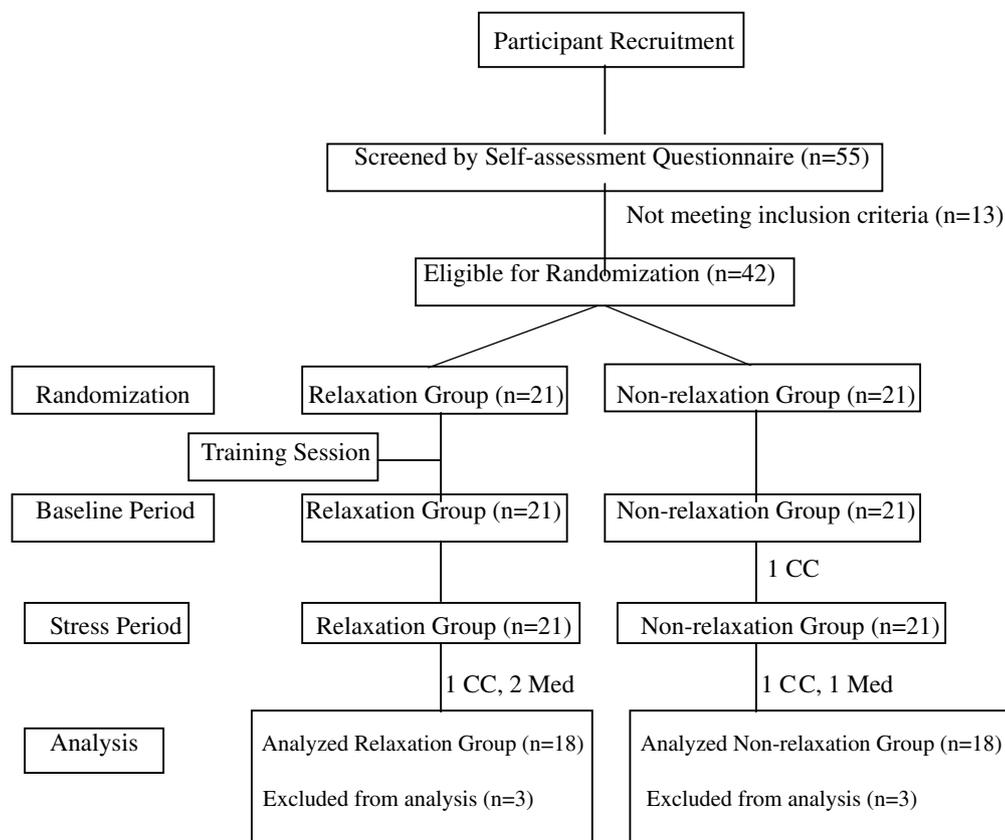
Fig. 1. Study flow diagram. 3 Subjects of each group were excluded from analyses, because they had suffered a common cold (CC) or had taken medication (Med) during the baseline period or the stress period.