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Acute psychological stress alerts the adaptive immune response: Stress-induced mobilization of effector T cells

Djordje Atanackovic [a,*], Benjamin Schnee [b], Gunter Schuch [a], Christiane Faltz [a], Julia Schulze [b], Cora S. Weber [b], Philippe Schafhausen [a], Katrin Bartels [a], Carsten Bokemeyer [a], Monika Christine Brunner-Weinzierl [c,d], Hans-Christian Deter [b]

[a] *Department of Oncology/Hematology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany*
[b] *Department of Psychosomatic Medicine and Psychotherapy, Charité Campus Benjamin Franklin, Free and Humboldt University, Berlin, Germany*
[c] *Deutsches Rheuma-Forschungszentrum Berlin, Berlin, Germany*
[d] *Department of Rheumatology and Clinical Immunology, Charité University Hospital, Humboldt-University of Berlin, Germany*

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Abstract

Influences of psychological stress on the acquired immune system have not consequently been investigated. We found acute psychological stress to cause an increase in $CD56^+$ and $CCR5^+$ effector T cells in the peripheral blood of healthy human subjects ($N=22$), while skin-homing CLA+ T cells decreased. At the same time, we observed a stress-induced decrease in CD45RA+/CCR7+ naive and CD45RA−/CCR7+ central memory T cells, while CD45RA−/CCR7− effector memory and CD45RA+/CCR7− terminally differentiated T cells increased. This T cell redistribution translated into an increase in T cells expressing perforin/granzyme B and in Epstein-Barr virus-specific, cytomegalovirus-specific and influenza virus-specific $CD8^+$ T cells. Thus, acute stress seems to promote the retention of less mature T cells within lymphoid tissue or skin while effector-type T cells are mobilized into the blood in order to be able to rapidly migrate into peripheral tissues.
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1. Introduction

Acute psychological stress exerts a number of characteristic effects on the human cellular immune system. Thus, it has repeatedly been shown that acute stress enhances the innate immune response by an increased mobilization of NK cells into the periphery (Ader et al., 2001). On the other hand, the effect of an acute stressor on T cells as key players of the acquired immune system has thus far not been examined systematically. A finding which seems surprising since the course of a number of T cell-mediated diseases is thought to be influenced by psychological stress (Kilpelainen et al., 2002; Kodama et al., 1999; Mohr et al., 2004).

T cells express adhesion molecules and chemokine receptors, which can be upregulated or lost during maturation, allowing T cells to coordinate their migratory routes with their immunological differentiation state (Jenkins et al., 2001). T cells have traditionally been divided into naïve and memory subsets according to their expression of CD45RA and CD45RO, respectively. It has become clear, however, that these markers do not provide a sufficient classification of the developmental state of T cells since CD45RA is re-expressed by terminally differentiated cells (Wills et al., 1999). It has recently been suggested that the pattern of expression of the lymph node homing receptor CCR7 and CD45RA divides human $CD4^+$ and $CD8^+$ T cells into distinct subsets (Sallusto et al., 1999). Both the CD45RA+CCR7+ “naïve” as well as the CD45RA−CCR7+ “central memory” fractions, in search for antigen, circulate between the peripheral blood and lymphoid

* Corresponding author. Tel.: +49 42803 5032; fax: +49 42803 2186.
E-mail address: D.Atanackovic@uke.uni-hamburg.de (D. Atanackovic).

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tissue. In contrast, CD45RA−CCR7− "memory effector" and CD45RA+CCR7− "terminally differentiated" effector T cells typically home into peripheral tissues in order to exert their effector function.

In the present study, we asked whether psychological stress alters the adaptive immune response by examining stress-related effects on peripheral T cell subsets as defined by their expression of a variety of adhesion molecules and chemokine receptors. Furthermore, we investigated whether possible stress-induced changes in peripheral numbers of these T cell subsets might have functional consequences for the T cell-mediated immune system, especially for the host's anti-viral defense. Finally, we examined in a preliminary analysis which hormonal mechanisms might be responsible for stress-related changes in the composition of peripheral T cell subsets.

2. Materials and methods

2.1. Test subjects

22 healthy male subjects (median age: 24 years, range 20–28 years) took part in our study. All test subjects were healthy nonsmokers and were not on medication. Subjects with potential malnutrition, alcohol abuse, strenuous physical exercise, strong mental stress on the test day or needle phobia were excluded. Test subjects were asked to refrain from eating and from drinking coffee or black tea after 10 p.m. the night before the test. The study protocol was reviewed and approved by the ethics committee of the University Hospital Benjamin Franklin.

2.2. Test procedure and cardiovascular parameters

All test subjects started the experimental procedure at 8.30 a.m. After written consent was obtained, a catheter was placed in a lower arm vein. The first blood sample was obtained at the end of a first "resting period" lasting for 25 min and served as the baseline value. Next, our computer-based mental stressor, which has previously been described in detail (Atanackovic et al., 2003), was started. The stressor consisted of a standardized computer based information-processing task to be completed using a tracking ball. It consists of two subtests, creates a purely mental stress situation and requires no physical movements. During the stress test, an increasing number of 3 to 11 clocks are presented to the test subjects who have to decide whether one or more hands of the clocks deviated more than 90° from the direction of an arrow shown on top of the screen. Wrong answers are indicated by a loud acoustic signal. At the end of the stress phase, which had a mean duration of 12 min, a second blood sample was collected ("stress" value). Following a second "resting" period, which lasted for another 20 min, the third blood sample was collected. Cardiovascular data were recorded continuously and were averaged for the first 5 min of each trial phase.

2.3. Questionnaires

As in our previous studies (Atanackovic et al., 2002), we used the German version of Spielberger's state-trait-anger-expression inventory (STAXI) (Schwenkmezger et al., 1992) to assess acute anger as an indicator of acute stress. Test subjects filled out the questionnaire before cardiovascular measurements were started, immediately following the "stress value" blood collection and 30 min later.

2.4. Flow cytometry and tetramer analysis

Peripheral blood mononuclear cells (PBMC) were isolated from heparinized blood by density gradient centrifugation and were stained with FITC-, PerCP- or APC-conjugated monoclonal antibodies to CD3, CD4, CD8 and CD56 (BD Biosciences, San Jose, USA) to determine lymphocyte subpopulations. To investigate the expression of chemokine receptors, adhesion molecules and other T cell differentiation markers, we performed co-staining with PE-conjugated monoclonal antibodies to CCR4, CCR5, CCR6, CXCR3, integrin β_7, CD62L, IL-7R, cutaneous lymphocyte antigen (CLA) (BD Biosciences) and CCR2 and CXCR5 (R&D Systems, Minneapolis, USA). IgG isotype controls were used in all experiments. Co-staining for CCR7 expression was performed by applying a mouse anti-human CCR7 IgM antibody followed by staining with a biotin-conjugated anti-mouse IgM (BD Biosciences) and streptavidin-PE (Immunotech, Marseille, France). To perform co-staining with anti-granzyme A and anti-perforin antibodies, PBMC were fixed using FACS Lysing Solution and permeabilized using Permeabilizing Solution followed by staining with appropriate antibodies (BD Biosciences).

Patients whose PBMC proved to express the HLA-A2 allele as analyzed by flow cytometry using the appropriate biotinylated monoclonal antibody (One Lambda Inc., Canoga Park, USA) and PE-conjugated streptavidin (Jackson Immunoresearch, Cambridgeshire, UK) underwent an analysis of peripheral numbers of virus-specific T cells using tetramer technology. HLA-A2 tetramers assembled with influenza matrix peptide 58–66 (GILGFVFTL), human cytomegalovirus (hCMV), pp65 peptide 495–503 (NLVPMVATV) and Epstein-Barr virus (EBV) BMLF1 peptide 280–288 (GLCTLVML) were kindly provided by Dr. Luescher at the Ludwig Institute for Cancer Research in Lausanne, Switzerland. PBMC in 50 μl PBS containing 3% FCS (Summit Biotechnology, Fort Collins, CO) were stained with PE-labeled tetramer for 15 min at 37 °C before addition of anti-CD8 and anti-CD3 mAbs for 15 min on ice. Four-color flow cytometry was performed using a FACSCalibur cytometer and CELLQuest software (BD Biosciences).

2.5. Real-time PCR analysis of hormone receptor expression

T cells of 10 healthy donors were separated into CD3+CCR7− and CD3+CCR7+ fractions using a flow cytometry-

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