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Journal of Neuroimmunology 158 (2005) 138 – 144

Journal of
Neuroimmunology

www.elsevier.com/locate/jneuroim

Social isolation stress exacerbates autoimmune disease in MRL/*lpr* mice

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Received 28 June 2004; received in revised form 30 August 2004; accepted 1 September 2004

Abstract

The potential physiological mechanisms explaining an influence of psychosocial stress on autoimmune diseases remain undetermined. Exposure of chronic social isolation stress to MRL/*lpr* mice significantly enhanced the degree of proteinuria after 20 weeks of age and reduced the survival rate. The serum anti-dsDNA IgG2a levels were increased significantly by stress at 19 weeks of age, which was simultaneously accompanied by inhibition of the serum corticosterone elevation. Furthermore, stress caused increased IFN-γ production from anti-CD3-stimulated splenic mononuclear cells, whereas IL-4 and IL-10 production decreased. These results indicated that isolation stress exacerbated autoimmune disease in MRL/*lpr* mice, the possible mechanism for which might be related to stress-induced dysregulation of Th1/Th2 balance and inhibition of the blood corticosterone response to inflammatory stimuli.
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Keywords: HPA axis; IFN-γ; IL-4; Nephritis; Psychosocial stress; SLE

1. Introduction

A long history of research has been done into the clinically meaningful link between psychosocial factors and autoimmune diseases (Rimón and Laakso, 1985; Urrows et al., 1994; Astin et al., 2002; Kung, 1995; Mohr et al., 2000; Thernlund et al., 1995). Recent observational studies and intervention trials have highlighted the hazardous role psychosocial stress plays in disease progression and the outcome of patients with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). One prospective study of patients with early RA found the experience of positive life events during the past year to be significantly related to a reduction in disability 1 year later (Parker et al., 1995). In another cohort study of women with SLE, negative life events in the preceding 6 months were correlated with reduced functional ability 8 months later (Costa et al., 1999). Moreover, recent randomized controlled trials have demonstrated that a cognitive–behavioral intervention for patients with a recent RA onset brought significant improvements in joint involvement (Sharpe et al., 2001, 2003). Psychoeducational intervention for SLE patients significantly improved physical function as well as patient self-efficacy and mental health (Karlson et al., 2003). Thus, accumulating clinical evidence has shown psychosocial stress to be related to a poorer prognosis in autoimmune diseases; however, the potential physiological mechanisms explaining such an association remain to be clarified.

Systemic autoimmunity in MRL/Mp-*lpr*/*lpr* (MRL/*lpr*) mice gives rise spontaneously to manifestations of autoimmune disease including nephritis, arthritis, and massive lymphadenopathy that resemble human SLE and, in some ways, human RA (Andrew et al., 1978; Putterman and Naparstek, 1994). The presence of homozygotes for the *lpr* gene, which have a defective allele of the apoptosis regulatory gene Fas, markedly accelerates the progression of autoimmune disease (Watanabe-Fukunaga et al., 1992). Various reports have shown that acceleration of autoimmune disease depends on T cells, especially on CD4+ helper T cells (Jabs et al., 1992; Jevnikar et al., 1994; Koh et al., 1995). The fact that MRL/lpr mice with a disrupted interferon (IFN)-γ gene develop milder autoimmune diseases as compared to intact MRL/lpr mice indicates that this cytokine is essential to the development of the diseases

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0165-5728/$ - see front matter. Published by Elsevier B.V.
doi:10.1016/j.jneuroim.2004.09.002

(Peng et al., 1997). In addition, high level expression of IFN-γ mRNA in the CD4+ T cells of intact MRL/*lpr* mice, as compared with an established long-lived substrain that lived almost twice as long and had delayed development of glomerulonephritis, was correlated with exacerbated progression of disease (Takahashi et al., 1996). Furthermore, IgG2a, whose secretion is stimulated by IFN-γ, is the dominant subclass of hypergammaglobulinemia and autoantibody in MRL/*lpr* mice (Peng et al., 1997; Balomenos et al., 1997). These results suggested that type-1 helper T cell (Th1) skewing of the immune response played an important role in accelerating the diseases.

Social isolation, such as by individual housing, can be used as a model to eliminate social interaction among animals, and has been reported to induce certain pathophysiological changes in rodents; for example, an increased or decreased response of the hypothalamus–pituitary–adrenal (HPA) axis and sympathetic nervous system (Kim and Kirkpatrick, 1996; Pashko et al., 1980; Huong et al., 1997; Mar Sánchez et al., 1998), acceleration of the development and growth of either transplanted or chemically induced tumors (Weinberg and Emerman, 1989; Kerr et al., 1997; Wu et al., 1999), and enhancement of small intestinal sensitivity to chemotherapy (Verburg et al., 2003).

The present study, based on the stress paradigm of social isolation, was done to examine the detrimental effect of psychosocial stress on an experimental autoimmune model, MRL/*lpr* mice and to attempt to clarify the mechanism(s) involved.

2. Materials and methods

2.1. Mice

Male MRL/MpJUmmCrj-*lpr*/*lpr* mice were purchased at the age of 5 weeks from Charles River Japan (Shizuoka, Japan). According to the method by Verburg et al. (2003) with some modification and immediately after arriving from the vendor, the mice were randomly assigned to group (control; n=4 per cage, floor space; 16×27 cm=432 cm^2, height; 13 cm) or individual housing (stress; n=1 per cage, floor space; 6×18 cm=108 cm^2, height; 12 cm). The floor space per mouse was the same (108 cm^2). A cardboard wall and a 4-cm distance were placed between any two cages housing individual mice, which resulted in a social isolation condition that allowed the animals to have relatively normal auditory and olfactory experiences, but not at any time to see, touch, or be touched by other animals in the colony. An animal laboratory maintained at a constant temperature (23–25 °C) with a 12-h light/dark cycle was used, and food and water were available ad libitum. This experiment was reviewed by the Ethics committee on Animal Experiments of the Graduate School of Medical Sciences, Kyushu University, and was carried out under the control of the Guidelines for Animal Experiments of the Graduate School of Medical Sciences, Kyushu University and the Law (No. 105) and Notification (No. 6) of the Government.

2.2. Measurement of serum corticosterone levels

Blood samples were collected from the retroorbital plexus between 0900 and 1100 h at the indicated time points, and plasma was frozen at −80 °C until analysis. The serum level of corticosterone was measured using commercially available RIA kit (ICN Biomedicals, Costa Mesa, CA). The concentration of corticosterone in the serum samples was calculated from a standard curve and expressed in nanograms per milliliter. The detection limit of the assay was about 1 ng/ml. In a preliminary experiment, our blood-drawing procedure without an anesthetic was confirmed not to induce an elevation of the serum corticosterone levels, probably because it was very rapidly performed (at most 1 min/mouse).

2.3. Measurement of proteinuria

To evaluate the severity of autoimmune disease, proteinuria, a surrogate marker of autoimmune nephritis, was measured by Uropaper II (Eiken, Tokyo, Japan). The protein concentrations were graded as follows: <29, 30–99, 100–299, 300–999, >1000 mg/dl. This grading method was applied to the present study because it has widely been used in clinical assessment (Burtis and Ashwood, 1999).

2.4. Determination of autoantibody and total immunoglobulin isotypes in serum

Serum IgG isotype specific to anti-double strand (ds) DNA was assayed by enzyme-linked immunosorbent assay (ELISA), as described previously (Furuya et al., 2001). Briefly, the ELISA plate was coated with 20 μg/ml dsDNA (Sigma, St. Louis, MO). Serially diluted serum samples were added to the plate. Each IgG isotype of the captured anti-dsDNA antibody was detected by peroxidase-conjugated rat antimouse IgG1 monoclonal antibody (MoAbs; ZYMED, San Francisco, CA), or biotin-conjugated rat antimouse IgG2a or IgG3 MoAbs (PharMingen, San Diego, CA) followed by peroxidase-conjugated streptavidin (PharMingen). Serum total IgG isotype was captured by coated antimouse IgG MoAbs (ZYMED), then detected as described above. The concentration of each total IgG isotype was determined by use of the individual immunogloblin standard (monoclonal mouse immunogloblin panel; ZYMED). The Ab titer of each dsDNA IgG isotype was calculated by comparing it with an internal standard as reported previously (Sudo et al., 1997). To make the standard serum, MRL/lpr mice raised under ordinary conditions were killed at the age of 10 weeks to collect the serum pool. This serum pool was used as the standard serum in the present study. The concentration of

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