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REVIEW ARTICLE

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Neuroendocrine-immune system in patients with rheumatoid arthritis

Abstract The neuroendocrine-immune system plays an important role in maintaining homeostasis. Since patients with rheumatoid arthritis (RA) tend to be exposed to long-term physical and psychological stress during the course of the disease, it is hypothesized that their neuroendocrine-immune system will become dysregulated. In order to understand the disturbances in the neuroendocrine-immune systems objectively, we measured and compared various components of the peripheral blood which were considered to reflect the state of these systems, in patients with RA and in control individuals. The serum levels of norepinephrine, interleukin-6 (IL-6), and the CD4/CD8 ratio were higher, whereas the levels of β-endorphin, adrenocorticotropic hormone, and NK cell activity were lower in the RA subjects than in the control subjects. On the other hand, the serum levels of methionine–enkephalin, epinephrine, corticotropin-releasing factor, cortisol, and CD57 were not significantly different in the two groups. In addition, we demonstrated the effects of hearty laughter, deep emotion with tears, or general anesthesia on the neuroendocrine-immune system. What need the most attention are changes in the IL-6 levels of RA patients. Serum IL-6 levels in RA were significantly higher than in controls, and fell rapidly to as low as half of their initial value after a bout of hearty laughter. Our results suggest that adequate mental intervention might serve to modulate the neuroendocrine-immune system of RA patients which had failed for various reasons.

Key words Brain reset mechanism · Emotional status · Heart laughter · Neuroendocrine-immune system · Rheumatoid arthritis (RA)

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Introduction

It has been reported that positive thinking and laughter have favorable effects on disease.[1] As physiological and psychological stress affect the endocrine system through the classical hypothalamic–pituitary–adrenal (HPA) axis, and there is an interaction between the endocrine and immune systems,[2] a better emotional status seems to modulate disease by affecting these systems. In other words, the immune system is influenced by mental stress, and its modulation affects the pathogenesis of a series of autoimmune diseases.

Rheumatoid arthritis (RA) is a chronic inflammatory disease in which autoimmunity is partially involved. Clinical findings relating to joints and the cervical spine, and various extraarticular manifestations such as vasculitis and pulmonary involvement, all have a negative effect on the well being of the patient. Psychoimmune processes are implicated in short-term changes in RA activity,[3] and RA patients frequently suffer stressful events at the onset of disease.[4] In healthy subjects, homeostasis is maintained by the complicated mechanisms that form a network involving various organ systems.[5,6] RA patients tend to be exposed to long-term physical and psychological stress during the course of their disease, and their neuroendocrine-immune system will become dysregulated, as has been reported elsewhere.[7–21]

The stress-response system consists of neural (psychological), endocrine, and immune components which interact with each other. Thus, humoral and cellular factors related to these components will be changed by psychological or physical stress. To evaluate the dysregulation of the neuroendocrine-immune system, we measured related parameters in the peripheral blood of RA patients and compared them with those in healthy subjects. In addition, we demonstrated the effects of hearty laughter or general anesthesia on the neuroendocrine-immune system. Here, we review our studies and discuss the relationship between mental condition and the neuroendocrine-immune system in RA patients and healthy individuals.

Neuroendocrine-immune mediators in RA patients and healthy subjects

In order to study the dysregulation of the neuroendocrine-immune system in RA, various mediators in the peripheral blood were measured.[22] Female RA patients were enrolled in this study from our outpatient clinic. Their average age was 58.0 years, and their average disease duration was 18.2 years. As a control, 54 healthy female volunteers were enrolled whose average age was 55.7 years. There was no significant difference in the average ages of RA and control individuals.

The plasma levels of β-endorphin, methionine–enkephalin (Met–enk), epinephrine, norepinephrine (NE), and dopamine were measured to assess the state of the nervous system. Corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), and cortisol levels, which are the main parameters related to the HPA axis, were evaluated for the endocrine system. The CD4/CD8 ratio, the ratio of CD57-positive cells, NK cell activity, and serum IL-6 levels were estimated for the immune system.

In RA subjects, serum levels of NE, dopamine, IL-6, and the CD4/CD8 ratio were higher than those of the controls, whereas the levels of β-endorphin, ACTH, and natural killer (NK) cell activity were lower. Serum levels of Met-enk, epinephrine, CRF, cortisol, and CD57 were not significantly different in the two groups (Table 1).

β-endorphin is one of the opioid peptides that is synthesized in the intermediate pituitary gland and lymphoid tissues, peripheral blood lymphocytes, and monocytes. β-endorphin has a strong analgesic effect on the neural system and suppressive effects on the immune system by binding to its specific receptor (δ- and μ-opiate receptors).[23–25]

In RA patients, the plasma levels of β-endorphin were reported to be lower than in healthy subjects[26] and osteoarthritis (OA) patients.[27] The mechanism is believed to be the reduction of ACTH secretion in RA patients irrespective of their use of corticosteroids. As ACTH has a common precussor (proopiomelanocortin) with β-endorphin, a decrease in serum ACTH level indicates a decrease in β-endorphin at the same time.

Peripheral blood levels of NE and dopamine, both of which are neurotransmitters of the sympathetic nervous system, were significantly higher in RA patients. This finding suggests that RA patients are under a condition of strain in which the autonomic nervous system, and particularly the sympathetic nervous system, is dominant. Among the items related to the endocrine system, only ACTH levels showed a significant difference between RA and control subjects. Serum ACTH levels in RA patients were lower than those in healthy individuals, as mentioned above.

In normal conditions, the production of ACTH and cortisol is up-regulated by stress. In addition, when inflammation occurs, proinflammatory cytokines, IL-1, and IL-6 activate CRF and ACTH at the hypothalamic level, resulting in a higher level of cortisol, that in turn suppress inflammation.[28] Whereas untreated RA shows higher serum levels of ACTH compared with healthy subjects, and those in treated RA patients are lower,[29] serum cortisol levels remain the same in each case regardless of treatment.

In contrast, in this study, the serum ACTH levels were significantly lower in RA patients than in healthy individuals. Nakamura et al.[30] have also reported a similar tendency regarding the serum ACTH levels in RA patients. We hypothesize that because the RA patients in this study had an extremly long disease history (average 18.2 years), their HPA axis might have fallen into a condition of chronic dysfunction due to the long-term use of steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and disease-modifying antirheumatic drugs (DMARDs).

A decreased CD4/CD8 ratio in the peripheral blood is found in patients with acquired immunodeficiency syndrome (AIDS),[31] acute viral diseases,[32] graft-versus-host disease (GVHD), and hemophilia,[33,34] and its deviations are substantial even among normal subjects. Although CD4-positive T cells are predominant in RA synovial tissue,[35] the CD4/CD8 ratios in peripheral blood are not well established.[36,37]

Table 1. Comparison of neuroendocrine-immune parameters between RA patients and healthy controls

	RA	*n*	Controls	*n*	*P*
β-endorphin (pg/ml)	3.1 ± 1.6	47	5.0 ± 1.8	54	<0.001
Methionine–enkephalin (pg/ml)	7.38 ± 3.45	47	7.82 ± 3.98	53	n.s.
Epinephrine (ng/ml)	0.041 ± 0.028	46	0.037 ± 3.98	49	n.s.
Norepinephrine (ng/ml)	0.504 ± 0.202	46	0.378 ± 0.217	49	<0.001
Dopamine (ng/ml)	0.020 ± 0.013	46	0.016 ± 0.013	49	<0.01
CRF (pg/ml)	12.73 ± 8.35	44	15.15 ± 8.16	51	n.s.
ACTH (pg/ml)	7.34 ± 6.95	49	24.18 ± 9.02	51	<0.001
Cortisol (μg/dl)	10.60 ± 4.37	48	9.69 ± 3.67	54	n.s.
CD4/CD8	2.23 ± 1.28	48	1.79 ± 1.01	53	<0.01
CD57 (%)	23.50 ± 16.05	46	21.77 ± 10.03	53	n.s.
NK cell activity (%)	33.2 ± 16.8	48	41.0 ± 13.4	53	<0.05
IL-6 (pg/ml)	33.57 ± 32.40	48	1.63 ± 1.98	54	<0.001

Values represent means ± SD. Statistical analysis was performed by the Mann–Whitney *U*-test
CRF, corticotrophin-releasing factor; ACTH, adrenocorticotrophic hormone; NK, natural killer; IL-6, interleukin-6; n.s., not significant

Although much remains to be clarified regarding the role of NK cells in RA,[38] NK cell activity is low in depressed patients[39] and patients with chronic fatigue syndrome,[40,41] and it decreases as a result of physical and psychological stress.[42,43]

It has been reported that various stresses increase plasma IL-6 levels in animals.[44–50] Patients affected with RA experience physical stresses arising from deformed joints, pain, disability, and the complications of the disease. At the same time, patients are believed to experience continuing mental stress due to anxiety and fear for the current condition and their future. This means that one of the reasons for the low NK cell activity and higher IL-6 levels in our RA group is their long-term stress.

The effects of hearty laughter on the neuroendocrine-immune system

Excessive physical or mental stress induces some types of disease in humans[51] and aggravates the disease activity of RA. It is known that stress causes atrophy of the thymus[52] in animals, and one of the mechanisms of this phenomenon is the suppression of the immune function via the autonomic nervous system or the endocrine system.[53] Under stressfull conditions, the lymphocyte subset is changed, mitogenic lymphocyte reactivity decreases, and NK cell activity is reduced.[54–58] In contrast, concentrations of IgA in the saliva and breast milk of mothers who have a good sense of humor is relatively high,[59] and they have a low incidence of upper respiratory tract infection.[60]

Furthermore, positive thinking and laughter have favorable effects on the musculoskeletal, circulatory, respiratory, nervous, endocrine, and immune systems, and simultaneously also help to relieve pain.[61,62] Based on this information, we investigated the effects of *rakugo*, an entertainment of traditional Japanese comic story-telling, as a means of improving the mental state of RA patients. Our preliminary studies showed that hearty laughter induced by *rakugo* affected the neuroendocrine-immune functions in patients with RA.[63,64] In this study, we measured NK cell activity, CD4/CD8 ratio, and IL-6 value in the peripheral blood as the immunological markers, and studied how eustress that was induced by the laughter in *rakugo* affected these three variables. We also compared these values with those of healthy subjects.

Eighty-three female patients with RA and 70 healthy individuals were studied. The average age and disease duration of RA patients were 55.8 years and 17.1 years, respectively. The average age was 57.6 years in the controls. In this experiment, all the subjects enjoyed the *rakugo* very much. It was performed by professional traditional Japanese comic story-tellers for an hour, and the audience really laughed whole heartedly. Peripheral blood samples were taken 1 h before and 30 min after the performance.

The base-line levels of the CD4/CD8 ratios and serum IL-6 levels were higher, and the NK cell activity was lower, in RA patients than in the control subjects. After the performance, IL-6 levels decreased in the RA group, whereas no significant difference was found in the control group (Table 2). The lower base-line NK cell activity in the RA group rose to the levels of the healthy controls after the performance, suggesting that NK cell activity was normalized by enjoying *rakugo*. Similarly, the higher CD4/CD8 ratios in RA patients fell to the levels of healthy control after the *rakugo* perfomance (Fig. 1). It is important to note that base-line serum IL-6 levels in the RA group were as much as eight times higher than in the control group, and fell rapidly to as low as half of their initial values after exposure to the *rakugo* perfomance. It should also be noted that the IL-6 values are closely related to the activity of the RA patients. We inferred from these results that hearty laughter has some favourable effects on the immune systems of RA patients, and modulates the disease activity. In other words, it is possible that hearty laughter can improve the clinical findings of RA. It has been reported that suppression of the IL-6 function by monoclonal antibodies against the IL-6 receptor is effective in the treatment of RA,[65] and a positive emotional state also has a therapeutic effect in RA.

In another recent study, the effects of very sad feelings, with tears, were evaluated in patients with RA.[66,67] As in the *rakugo* study, peripheral blood was taken to measure the NK cell activity, the CD4/CD8 ratios, and the IL-6 levels before and after a very sad and sentimental Japanese human-interest story. Contrary to expectations, the results were the same as those after hearty laughter.

It was suggested that a strong feeling induced by a story, whether it is funny or sad, is recognized by the cerebral cortex in the same way, and acts as a negative stressor by matching it with the listeners' emotional memories in the limbic system following a temporal resetting of the limbic system, including the hypothalamus, thereby modulating the neuroendocrine-immune system. We therefore propose to name this phenomenon the brain reset mechanism.

Table 2. Comparison of immune parameters between RA patients and healthy controls

	Before exposure			After exposure		
	RA (n = 83)	Controls (n = 70)	P	RA (n = 83)	Controls (n = 70)	P
NK cell activity (%)	33.2 ± 15.7	40.7 ± 13.3	<0.01	37.8 ± 14.9	41.2 ± 12.8	n.s.
CD4/CD8	2.36 ± 1.29	1.87 ± 0.99	<0.01	2.19 ± 1.26	1.88 ± 0.96	n.s.
IL-6 (pg/ml)	29.7 ± 29.1	1.70 ± 1.84	<0.001	16.3 ± 24.5	1.95 ± 2.20	<0.001

Values represent means ± SD. Statistical analysis was performed by the Mann–Whitney U-test

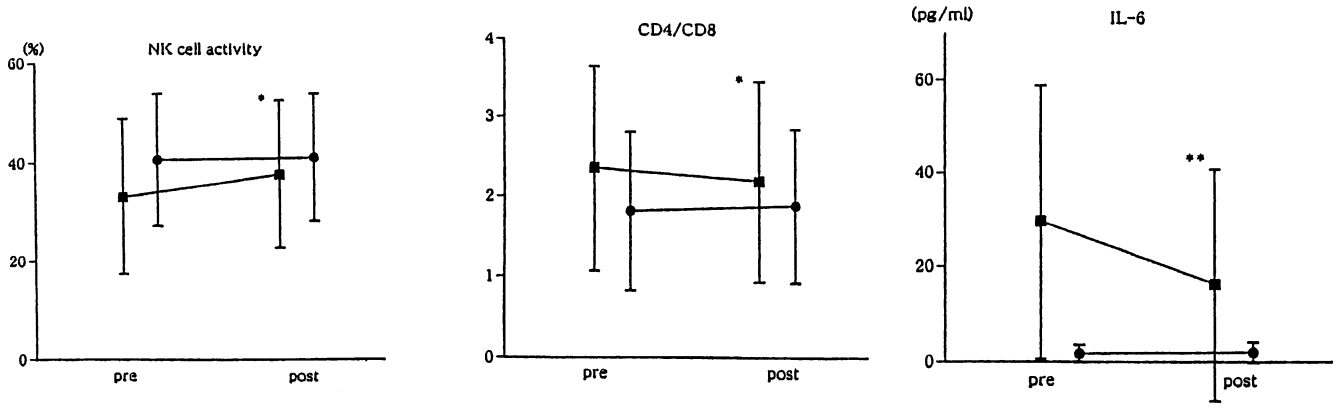

Fig. 1. Changes in the serum levels of NK cell activity, CD4/CD8 ratio, and IL-6 before and after exposure to hearty laughter. Data are shown as mean ± SD. Findings were statistically analyzed using Wilcoxon's signed rank test. *Squares*, rheumatoid arthritis; *circles*, controls; *NK*, natural killer. $*P < 0.01$; $**P < 0.001$

The effects of anesthesia on the neuroendocrine-immune system

We then studied the effects of general anesthesia on the neuroendocrine-immune system to investigate the relationship between stress and the neuroendocrine-immune system from a different point of view.[68] We believe that patients who are about to undergo surgery are under excessive mental stress due to anxiety or fear. Conversely, during the period from the administration of anesthesia to just prior to the operation, the patients are assumed to be free from mental stress.

Patients with RA or OA who needed total knee or hip arthroplasty under general anesthesia were enrolled in the study. The levels of IL-6, epinephrine, NE, dopamine, CRF, and cortisol were measured in the peripheral blood.

In RA patients, the levels of IL-6, cortisol, and epinephrine were significantly higher than the base-line levels before anesthesia when the patients were under severe mental stress. However, as soon as general anesthesia was administered, serum levels of IL-6, cortisol, and epinephrine decreased significantly compared with the levels before anesthesia. Such changes were not apparent in patients with OA. The levels of other substances in the peripheral blood which are known to be related to stress, such as CRF, dopamine, and NE, showed no changes in patients with RA or OA.

From the results of these experiments, we considered that neuroendocrine-immune dysfunction in RA patients could be modulated by what we call the "brain reset mechanism."

Conclusions

Dysregulation of the immune system is involved in the pathogenesis of RA, and in addition, long-term mental stress modifies immunological interactions. Moreover, as the immune system is closely related to the neuroendocrine system, dysregulation of the neuroendocrine-immune system exists in RA. Based on these facts, and empirical experience that a balanced psychological state is good for health, we hypothesized that mental intervention might alter the pathophysiology of the disease.

Our results suggested that adequate mental intervention is preferable for the treatment of RA, and excessive mental stress should be eliminated. It was also revealed that the neuroendocrine-immune system mediates the modification of disease activity. Therefore, mental support is a necessary and important therapy in the treatment of RA. We also believe that during an examination, taking the psychological state of a patient into consideration relieves mental stress and is effective in treating RA patients, and that structuring their daily life with the motto "cheerfully and positively" is important.

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