Effect of general anesthesia on the abnormal immune response in patients with rheumatoid arthritis

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Abstract

Objective

To evaluate the influence of mental stress on the neuroendocrine-immune system in patients with rheumatoid arthritis (RA).

Methods

Twenty-four patients with RA and 10 patients with osteoarthritis (OA) who underwent total knee or hip arthroplasty under general anesthesia were enrolled in this study. The blood levels of interleukin-6 (IL-6), IL-1 receptor antagonist (IL-1Ra), tumor necrosis factor-α (TNF-α), soluble TNF receptors (TNF-Rs) and other substances related to stress were measured just before administering anesthesia on the day of the operation when the patients lay on the operating table and roughly 30 min later when the patients were under general anesthesia without mental stress. These values were compared with those at the same time on the day before the operation, which were considered as controls.

Results

In patients with RA under general anesthesia, the levels of IL-6, TNF-α, and TNF-R1 and TNF-R2 in the peripheral blood were significantly decreased compared with the levels before anesthesia ($p < 0.01$). Before anesthesia the levels of IL-1Ra in the peripheral blood were significantly higher, and the level of IL-1Ra was enhanced after the administration of general anesthesia, when compared with the level on the day before the operation ($p < 0.01$). Such changes were not apparent in patients with OA.

Conclusion

In patients with RA, excessive mental stress should be eliminated to modify the interaction between the stress-immune system and stress-endocrine system as a method to better control disease activity.

Key words

Rheumatoid arthritis, mental stress, neuro-endocrine-immune system, interleukin-1 receptor antagonist, interleukin-6.

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Introduction

A growing body of research indicates that activation of the "stress-related" neuro-endocrine system and its interactions with the immune system play pivotal roles in the etiology and progression of the rheumatic diseases (1). It is also clinically accepted that not only environmental factors but also psychological stress can often result in the development or exacerbation of various rheumatic diseases (2, 3).

Rheumatoid arthritis (RA) is an autoimmune disease characterized by the infiltration of various cytokine-producing leukocyte subpopulations into both the developing pannus and the synovial space. The etiologic cause of RAis not clearly understood, but pro-inflammatory cytokine-mediated autoimmune responses are considered to play a crucial role in the pathogenesis of RA (4). The chronic nature of this disease results in multiple joint inflammation with subsequent destruction of the cartilage and joints. Thus, patients with RA are subject to physical stress caused by joint deformities, pain, cervical disorders and various other complications. Although we often observe that disease activity in RA patients worsens after severe mental stress, the underlying mechanism remains unclear.

We have already proposed that mirthful laughter, which may influence the interaction between mental stress and the neuro-endocrine-immune system, affects the disease activity of RA(5, 6). Serum concentrations of interleukin (IL)-6, which plays a critical role in the pathogenesis of RA, were dramatically decreased after exposure to mirthful laughter. These results suggest that psycho-immune processes may be implicated in short-term changes in RA disease activity. These results also raise the possibility that the mental condition of RA patients is greatly influenced by several forms of stress. This notion is supported by the fact that the serum level of IL-6 in RA patients is also decreased by general anesthesia, since patients who are about to undergo surgery are under excessive mental stress due to anxiety or fear when they are on the operating table which general anesthesia would eliminate (7).

In this study, we examined in detail the neuro-endocrine-immune system of RA patients under excessive mental stress because awaiting surgery, and investigated whether the suppression of mental stress by general anesthesia normalized their neuro-endocrine-immune system.

Materials and methods

Patients.

Patients with RA were diagnosed according to the revised criteria of the American College of Rheumatology (8). Most patients were receiving disease modifying anti-rheumatic drugs, but none were receiving predonisolone at a dose of >5 mg/day. All patients were hospitalized at the Nippon Medical School for total knee or hip arthroplasties under general anesthesia. We obtained informed consent from all the patients included for participation in this study. All the experiments complied with the regulations of the Ethical Committee of Nippon Medical School and Japanese law. No clinical complications under general anesthesia were experienced by these patients. The characteristics of the patients with RA and OA are summarized in Table I. Systemic disease activity was assessed using an arbitrary index based on the scoring system described by Wahle *et al*. (9) and most of the patients were found to have low or moderate activity.

Blood sampling

As controls for each immunological marker examined, peripheral blood samples were collected from the subjects at 8:30 am (indicated as I) on the day before the operation. Peripheral blood samples were also collected just before anesthesia was administered on the day of the operation when the subjects lay on the operating table at 8:30 AM (indicated as II). It is considered that it takes about 30 minutes for general anesthesia to be induced and the patients to be prepared for the operation; during this period mental stress inducing stimuli to the cerebral cortex and limbic system are suppressed or blocked. A blood sample was collected again at around 9:00 AM, just before commencement of the operation (indicated

Table I. Background of patients with rheumatoid arthritis (RA) and osteoarthritis (OA) (values expressed as the mean ± SE).

Parameter	RA	OA
Number of patients	24	10
Gender (male/female)	4/20	2/8
Mean age (yrs.)	64 ± 1.2	68.0 ± 4.8
Duration of disease (yrs.)	22.5 ± 3.9	ND
C-reactive protein (mg/dl)	2.3 ± 1.5	< 0.4
Corticosteroids (no. of patients)	19	0
NSAIDs (no. of patients)	20	6
DMARDs (no. of patients)	18	0

DMARD: disease modifying anti-rheumatic drug; NSAID: non-steroidal anti-inflammatory drug.

as III). Sevoflurane and propofol were used as the general anesthetic agents, and vecuronium bromide was used as the muscle relaxant.

Anti-rheumatic drugs, including steroids and pre-medications for anesthesia, were all administrated on the morning before and on the day of the operation. Following the operation all of the RA patients were treated in our department with an adequate dose of corticosteroid (hydrocortisone 100 mg on days 1 and 2, 50 mg on day 3, and 25 mg on day 4). We believe that this steroid dosage would not have affected the levels of serum epinephrine, cortisol, and various cytokines since the patients were treated with corticosteroid just after the operation. We determined their mental condition by administering a questionnaire after the operation as previously described (7). In this mental status questionnaire survey, items numbers 1 to 5 measure anxiety, worry, or fear, that is to say "mental stress." We classified the degree of mental stress into 4 ranks. The severe stress group is more than 4 items, moderate stress is 3 items, mild stress is 2 items, and little stress is one item or none.

Quantitation of serum cytokine levels and stress related substances.

The levels of cytokine in the serum were measured using cytokine specific ELISA kits for TNF-α, IL-1 receptor antagonist (IL-1Ra), and soluble TNF receptors (Quantikine, R&D Systems, Minneapolis, MN). The detection sensitivity of TNF-α, IL-1Ra, and soluble TNF receptors were 0.5 pg/ml, 47 pg/ml, and 78 pg/ml, respectively. IL-6, cortisol, corticotrophin releasing hormone (CRF), epinephrine, norepinephrine, and dopamine were measured as previously described (7).

Statistical analysis

The Wilcoxon signed-rank test was performed to determine the statistical significance of the results. A p value < 0.05 was considered as statistically significant.

Results

Serum concentrations of pro-inflammatory cytokines in patients with RA were decreased after the administration of general anesthesia

To determine whether psychoimmune processes were involved in short term changes in RA disease activity, we examined in detail the neuro-endocrine-immune system of RA patients with excessive mental stress. To examine this, we selected patients with RAwho were scheduled for surgery since in general they are under excessive mental stress due to anxiety or fear and general anesthesia is expected to eliminate it. We also performed mental-questionnaire-survey to measure anxiety or fear (Table II), and obtained similar results as demonstrated by Hirano *et al.* (7). In the mental-questionnaire survey, 27 from the total of 34 patients (including RA and OA) were "severe" and 7 patients were in the "moderate" group. There were none in the "mild" and "little" groups. These results show all the patients had mental stress of more than moderate grade, but among these patients only 7 (5 with RA and 2 with OA) were hopeful for a successful operation. In all 6 variables, there was no significant difference between the severe and the moderate group. Accordingly, it was determined that at around 8:30 AM, just before anesthesia was administered (indicated as IU) all the patients were under excessive mental stress. Therefore, we investigated whether the suppression of mental stress by general anesthesia would normalize the neuro-endocrine-immune system of RApatients.

Because diurnal variation cannot be bypassed, we collected blood samples on a fixed time as possible as we can. In RA patients, at 30 minutes after administration of the general anesthesia and just before commencement of the operation, the IL-6 levels in the

Table II. Mental-questionnaire-survey.

What did you feel while you were lying on the operating table and were about to be administered anesthesia ? Please check items which correspond to your feelings.

1. [ ] Will the anesthesia work effectively?
2. [ ] Will the pain in my joints be relieved by the operation?
3. [ ] Will I be able to walk after the operation?
4. [ ] Will I be able to use my arms freely after the operation?
5. [ ] Will my movements in daily living become easier after the operation?
6. [ ] I will be comfortable after falling asleep and waking up later.
7. [ ] I will finally be relieved from pain in my joints.
8. [ ] I will finally be able to walk properly.
9. [ ] I will finally be able to use my arms freely.
10. [ ] My movements in daily living will finally become easier than they were before the operation.

blood were 11.8 ± 3.1 pg/ml, which represented a significant decrease compared to the levels of 30.8 ± 11.1pg/ml observed just before administration of the general anesthesia ($p < 0.01$). In the OA patients, however, there were no significant changes in the level of serum IL-6 (Figure 1a). This result is consistent with our previous observation that the serum IL-6 levels were decreased after the exposure to anesthesia (7). We next examined the changes in serum TNF-α, which may be the most critical pro-inflammatory cytokine in the pathogenesis of RA (10, 11). In RA patients, the TNF-α levels in the blood were also significantly decreased after the administration of the general anesthesia compared to the levels just before administration of the general anesthesia. However, in patients with OA, there were no significant changes in the levels of serum TNF-α (Fig. 1b).

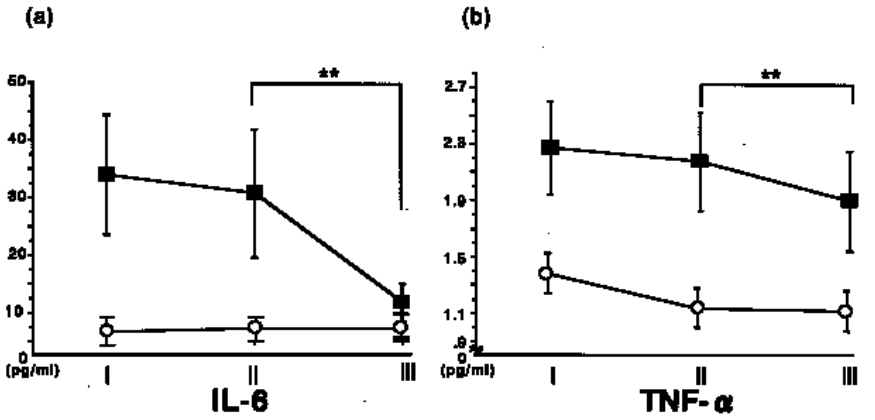

Fig. 1. Changes in serum concentrations of pro-inflammatory cytokines in patients with RAafter the administration of general anesthesia. Because diurnal variation cannot be bypassed, we collected blood samples on a fixed time as described below. Peripheral blood samples were collected from the subjects at 8:30 AM (indicated as I) on the day before the operation, just before anesthesia at 8:30 AM (indicated as II), and about 30 min after the administration of general anesthesia (just before the commencement of the operation, indicated as III). All of RApatients were covered with an adequate dose of corticosteroid after the operation in our department. The levels of pro-inflammatory cytokines were measured as described in the materials and methods. Data represent mean values ± SEM. **P< 0.01. ■ RA; ❍ OA.

Changes in the levels of serum anti-inflammatory cytokines in patients with RA after exposure to general anesthesia

As demonstrated above, the levels of pro-inflammatory cytokines in the serum were significantly decreased by the administration of general anesthesia. Therefore, we also examined whether the administration of general anesthesia would influence the levels of serum anti-inflammatory cytokines in patients with RA. Interestingly, there was significant difference in the level of serum IL-1Ra, which is a natural inhibitor of IL-1 (12,13), when comparing the levels on the day before operation and the levels just before anesthesia ($p < 0.01$). A further increase was observed in serum IL-1Ra concentrations after the administration of general anesthesia. In the OA patients, however, there were no statistical changes in serum IL-1Ra concentrations (Fig. 2a). In contrast, mean serum sTNF-R1 and sTNF-R2 concentrations after the administration of general anesthesia were significantly decreased as compared with the levels just before the administration of general anesthesia ($p < 0.01$). In patients with OA, there were no significant changes in the serum levels of sTNF-R1 and sTNF-R2 (Fig. 2b and c).

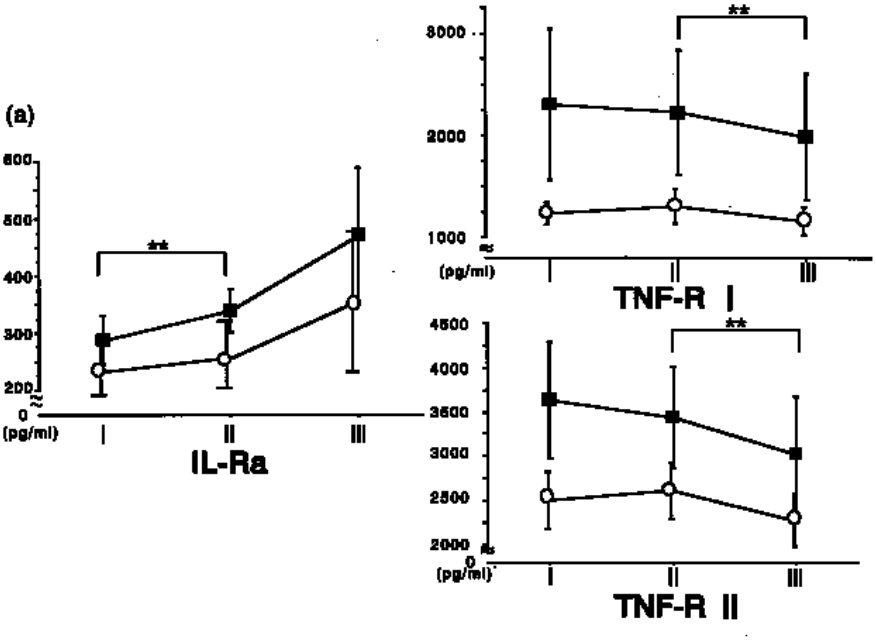

Fig. 2. Changes in serum concentrations of anti-inflammatory cytokines in patients with RAafter the administration of general anesthesia. Peripheral blood samples were collected as described in Figure 1, and the levels of anti-inflammatory cytokines were the measured as described in the materials and methods. Data represent mean values ± SEM. **P< 0.01. ■ RA; ❍ OA.

Changes in neuro-endocrine system in patients with RA after the exposure to general anesthesia

We also examined several neuro-endocrine parameters. Consistent with our concept that patients with RA who are about to undergo surgery are normally under excessive mental stress, we found that there was a significant increase in the levels of epinephrine just before the administration of general anesthesia and the serum epinephrine levels were significantly decreased after the administration of general anesthesia. Interestingly, in RA patients, there was hardly any change in the cortisol levels, which is known as a major stress-related hormone. This result reflected the use of exogenous corticosteroid since production of endogenous

Table III. The changes in the levels of stress-related substances in the peripheral blood of patients with RAand OA.

	I	II	III
CRF, pg/ml			
RA	5.3 ± 0.5	5.6 ± 0.7	5.0 ± 0.6
OA	6.5 ± 0.6	8.8 ± 1.4	6.1 ± 1.2
Cortisol, μg/dl			
RA	8.0 ± 1.2	7.1 ± 1.3	6.0 ± 1.3
OA	36.9 ± 4.8	29.8 ± 8.3	32.0 ± 11.2
Epinephrine, pg/ml		a / b	
RA	c: 24.0 ± 3.8	38.0 ± 4.4	15.9 ± 1.4
OA	c: 56.4 ± 9.7	50.4 ± 9.3	21.0 ± 2.1
		d	

I: 8:30 am (the day before the operation); II:8:30 am (just before anesthesia); 9:00 am (under anesthesia for 30 min).
a: significant differences between I and II; b,d: significant differences between II and III; c: significant differences between RAand OA. b: $p < 0.01$; a, c, d: $p < 0.05$.
Data represent mean values ±SEM.

corticosteroid is usually suppressed by the long-term administration of exogenous corticosteroid. Consistent with this notion, the level of serum cortisol in RA patients was significantly lower when compared with that in OA patients. These results suggest that cortisol would not be a good item to evaluate stress condition in patients who are treated with corticosteroid. Other items measured in this study are summarized in Table III.

Discussion

Autoimmune disease is explained in terms of an imbalance of the immune system and treatment is based on re-establishing this balance. Cytokines play central roles in the pathogenesis of imbalance of the immune system. We have already demonstrated that mirthful laughter affects serum IL-6 levels in patients with RA by the suppression or blockade of the neuro-endocrine-immune system (5-7,14), indicating that the immune system is modulated by positive emotional conditions. Recent evidence that the monoclonal antibody against the IL-6 receptor is effective in the treatment of RA (15,16), suggesting that a positive emotional state may also have some therapeutical effect in RA.

In the present study, we present evidence that general anesthesia, which may influence the neuro-endocrino-immune system, also affects IL-6 levels in patients with RA. In addition to IL-6 levels, the serum level of TNF-α, that may be a most crucial pro-inflammatory cytokine for the pathogenesis of RA (10, 11), was also significantly decreased by the general anesthesia. Interestingly, an increase in anti-inflammatory molecules such as IL-1Ra was also observed after the administration of the general anesthesia. Consistent with our results, it has been shown that external stress i.e. psychological stress, which is known to be accompanied by HPA-axis hyperactivity and increased catecholaminergic turnover, is also accompanied by an increased production of pro-inflammatory cytokines (17-19). It has been shown that anesthesic drugs tend to depress neuronal firing and excitatory synaptic transmission (20) and potentiate synaptic inhibition. We consider that anesthesia can suppress the transduction of stress information to the immune and endocrine system. Therefore, our results not only support the concept that patients with RA are usually under mental stress, but also indicate that the modulation of the emotional state by general anesthesia may be one of alternatives to help current therapeutic strategies for RA.

In the present study, we also evaluated the serum levels of soluble TNF-Rs. In contrast to the increase of IL-1Ra by the general anesthesia, soluble TNF-Rs decreased in parallel with the decrease of TNF-α. Therefore, this decrease in soluble TNF receptor levels might reflect the decrease in the serum concentration of TNF-α.

The underlying mechanism by which mental stress and general anesthesia affect the immune system remains unclear. There is a possibility that general anesthesia by itself affects cytokine production. However, this is unlikely since several studies have demonstrated that general anesthesia does not influence serum cytokine concentration (7, 21). Another possibility is that the neuro-endocrine system directly influences the immune system. It is becoming increasingly clear that there exists a bi-directional communication between the neuro-endocrine system and the immune system (1, 22).

In our study this neuro-immune cross-talk might have been affected by general anesthesia. The key molecules of the neural system are catecolamines. Monoamines, such as catecholamines and pro-inflammatory cytokines are considered among the principal messengers responsible for the bi-directional communication between the central nervous system and immune system. A significant decrease in the levels of epinephrine in the sympathetic nerve-adrenal medullary system, which is one of the most important stress reaction systems, was observed just after the anesthesia in patients with RA. However, a similar decrease was also observed in patients with OA. Therefore, it is difficult to state that epinephrine directly modulated the immune system. Our preliminary experiments suggest that changes in the expression of catecolamine receptors may explain our observations. These results demonstrated that the expression of catecholamine α- and β-receptors on immune cells (especially on B cells) from RA patients but not from OA patients were upregulated after the administration of general anesthesia (our unpublished data). In fact, Wahle and colleagues have demonstrated that β2-adrenergic receptors on B cells from patients with RA were downregulated when compared with those from normal subjects (23). Consistent with this notion, recent re-

ports have demonstrated that lymphocytes and macrophages have β2-adrenergic receptors, and epinephrine as well as norepinephrine exert their regulatory influence on immune cells via these receptors (24, 25). Under normal physiologic conditions β2-adrenergic agonists inhibit many immune responses. They inhibit the T cell proliferative response, and down regulate the IL-2 receptor on activated T cells as well as IL-2 production. Moreover, catecholamines inhibit B cell proliferation, antibody secretion as well as cytotoxic T cell and natural killer cell responses (26). Furthermore, Heijnen CJ and colleagues have demonstrated that secretion of IL-6 from PBMC in response to α-adrenergic agonist from patients with juvenile idiopathic arthritis was different depend of the activity of disease (27). An unresponsiveness of leukocytes to catecholamine should theoretically lead to uncontrolled, flamboyant immune responses, as in the case of chronic inflammatory arthritis. Further investigations are needed to confirm the effect of anesthesia on the expression of the catecholamine receptors.

It is widely agreed that long-term administration of corticosteroid suppresses the secretion of endogenous cortisol. Therefore, the levels of cortisol in RA patients were suppressed by oral administration of corticosteroid since most of RA patients but not OA patients received corticosteroid as shown in Table I. Therefore, oral administration of corticosteroid usually altered the reactivity of HPA axis. In addition, it has been shown that basal concentrations of dehydroepiandrosterone and its sulfate, were found to be significantly lower in pre-menopausal patients with RAwho were not treated with corticosteroid than in controls (28), suggesting that adrenal gland in patients with RA is intrinsically hypofunctional. Therefore, it may be difficult to evaluate in detail the reactivity of HPA axis in patients with RA. Consistent with this, It is not clear why the levels of epinephrine were higher in OA group at time I in compared with those in RA group as shown in Table I. Possible explanation for this difference may be explained by the fact that RA patients but not OA patients usually have an operation several times because of the destruction of multiple joints. However, when they were on the operating table, both OA and RApatients were equally under excessive mental stress. Further examination should be carried out to clarify this issue.

In conclusion, our results indicate that a positive emotional state such as mirthful laughter and general anesthesia affects the immune system, and has beneficial effects for controlling RA.

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