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Psychoneuroimmunology of the mind and body

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Abstract. Over the last several decades, increased attention has been given to psychoneuroimmunology investigation of the putative physiological mechanisms underlying mind and body interaction. In addition to presenting novel interdisciplinary evidence, this review discusses psychosomatic disease, stress biomarkers, and recent clinical and basic research into psychoneuroimmunology. When functioning normally, the response of the neuro–endocrine–immune systems to stress results in the maintenance of homeostasis of the organs. However, dysfunction of such physical systems in response to stress may lead to psychosomatic disease. Clinically, several stress biomarkers have been shown to be useful for the measurement of the degree of physical response to stress, including several neurotransmitters, hormones, cytokines, and other materials from the neuro–endocrine–immune systems. A large number of observational studies and clinical trials have clearly shown that chronic, real life stress suppresses immune function and exacerbates autoimmune and allergic disease. We have recently used mouse models of these diseases to show that hyporesponsiveness of the hypothalamus–pituitary–adrenal axis is critical to such stress-induced exacerbation.

Keywords: Autoimmune disease; Allergic disease; Psychosocial stress; Psychosomatic disease

1. Introduction

Over the past several decades, "psychoneuroimmunology (PNI)" has increased in popularity worldwide, with numerous researchers investigating the physiological mechanisms behind mind and body interaction [1]. This novel interdisciplinary field includes psychology, neurology, endocrinology, and immunology. In this review, we discuss psychosomatic disease, stress biomarkers, and recent clinical and basic research on PNI for the purpose of delineating the PNI relationships of the mind and body.

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2. What is psychosomatic disease?

As shown in Fig. 1, stress is classified by DSM-IV-TR [2] into axis-I and is referred to as "psychological factors affecting medical conditions". Patient characteristics such as alexithymia, overadaptation, and a disease-prone personality are classified into axis-II. These pathologies may eventually lead to acting out (e.g. absent from school, antisocial behavior), psychological dysfunction (e.g. anxiety disorders, depression) in axis-I, or physical dysfunction in axis-III. "Psychosomatic disease" is defined as a stress-induced physical dysfunction, representative of which are bronchial asthma, hyperventilation syndrome, essential hypertension, atrial fibrillation, peptic ulcer, functional dyspepsia, irritable bowel syndrome, hyperthyroidism, diabetes, migraine, chronic pain, torticollis, rheumatoid arthritis, atopic dermatitis, chronic urticaria, and pollakiuria. In contrast, if stress-induced frustration can be ventilated by a hobby, sport, or other outlet, health is maintained.

3. Stress biomarkers

Stress biomarkers are as follows: the first is the nervous system markers, such as catecholamines; adrenaline, noradrenaline, and dopamine in the blood, urine, and saliva. The second is the endocrine system markers, such as corticoids (cortisol, 17-hydroxycorticosteroid and aldosterone) in the blood, urine and saliva, and ACTH in the blood. The third is the immune system markers, such as the number of total lymphocytes and lymphocyte subsets such as T cells, B cells and natural killer (NK) cells, the activity of NK cells, mitogen reactivity, immunoglobulin (IgA, IgM, IgG, and IgE), and cytokines such as interleukin (IL)-1, IL-2, IL-6, interferon (IFN) and tumor necrosis factor (TNF). In addition, these biomarkers can change to other forms of stress, depending on the kind and duration of the initial stress.

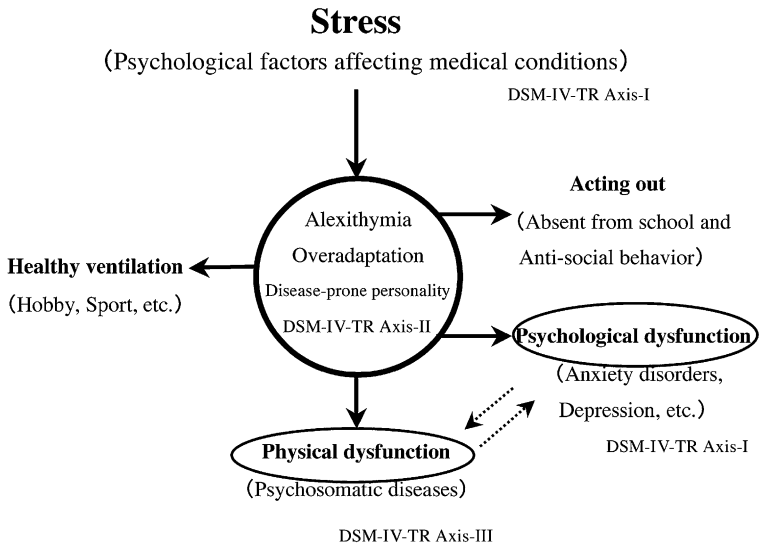

Fig. 1. The psychological or physical response to stress in humans.

In addition to central nervous system regulation of peripheral cytokines, peripheral cytokines have a crucial effect on central nervous function. For example, the influences of IL-1 are fervescence, anorexia, and slow-wave sleeping. TNF, IFN, and related cytokines also affect nervous and endocrine function such as fervescence, anorexia, slow-wave sleeping and analgesia.

4. Clinical research on PNI

While acute stress may be associated with transient immune activation, as shown in Table 1, chronic or real life stress seems more consistently associated with immune suppression. Bartrop et al. reported that the death of a spouse reduced T cell function. Moreover, Schleifer demonstrated that the death of a spouse reduced lymphocyte mitogen-responses. More notably, in the New England Journal of Medicine, Cohen et al. reported that mental stress increased the morbidity rate from the common cold.

5. Basic research on PNI

Currently, our laboratory is investigating the precise physiological mechanisms behind mind and body interaction, and our observations have been reported in several journals [3–

Table 1
Suppression of immune function by stress

Author (Journal)	Year	Type of stressor	Results
Ironson et al. (*Psychosom. Med.*)	1997	Natural disaster (hurricane)	Reduced NK cell activity
Cohen et al. (*New Engl. J. Med.*)	1991	Mental stress	Increased morbidity rate from common colds
Kronfol et al. (*J. Affect. Disord.*)	1986	Depression	Reduced lymphocyte response
Thomas et al. (*Am. J. Psychiatry*)	1985	The elderly without social support	Reduced lymphocyte PHA response
Schmidt et al. (*J. Fam. Pract.*)	1985	Loss experience, interpersonal stress	Increased herpes labialis recurrence
Schleifer et al. (*JAMA*)	1983	Death of a spouse	Reduced lymphocyte PHA and PWM response
Gottschalk et al. (*Psychother. Psychosom.*)	1983	Worry or depression with changes in life	Reduced NK cell activity
Dorian et al. (*Clin. Exp. Immunol.*)	1982	Certification examination	Reduced lymphocyte PHA response
Green et al. (*Psychosom. Med.*)	1978	Effect of stress due to changes in life	Reduced cytotoxic function
Bartrop et al. (*Lancet*)	1977	Death of a spouse	Reduced T cell function
Palmbland et al. (*J. Psychosom. Res.*)	1976	Sleep disorder	Reduced phagocytic capacity against streptococcus, reduced production of interferon
Meyer et al. (*Pediatrics*)	1962	Chronic daily stress	Reduced resistance to streptococcal infection
Jacob et al. (*Munch. Med. Wochenschr.*)	1962	Mental and social stress	Increased morbidity rate by upper bronchial infection

PHA=phytohemagglutinin; PWM=pokeweed mitogen.

9]. Herein, the results of our study on the effect of stress on autoimmune and allergic diseases are presented.

(1). The effect of stress on autoimmune disease

First, we reviewed recent prospective observations and randomized controlled trials (RCTs) that investigated the effect of psychosocial stress on autoimmune diseases, such as systemic lupus erythematosus (SLE), multiple sclerosis (MS) and rheumatoid arthritis (RA). As shown in Table 2, all of the five prospective observations exhibited positive data and two of the three RCTs showed positive data. Although these results indicate a close association between stress and autoimmune diseases, the precise physical mechanisms underlying such an association remain to be identified.

In a study [8] using a mouse model of autoimmune disease, MRL/*lpr* mice, exposure to chronic social isolation stress from the age of 5 weeks significantly enhanced the degree of proteinuria after 20 weeks of age and reduced the survival rate. The increase of serum anti-dsDNA IgG2a levels was significantly accelerated by stress at 19 weeks of age and was simultaneously accompanied by inhibition of 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. Possible mechanisms include stress-induced dysregulation of the Th1/Th2 balance and the inhibition of blood corticosterone response to inflammatory stimuli.

Table 2
The effect of stress on autoimmune disease

Author (Journal)	Year	Sample (Disease)	Duration	Design	Results
Sharpe et al. (*Rheumatology*)	2003	53 (RA)	18 months	RCT	**Positive:** Cognitive–behavioral intervention significantly improved joint symptoms.
Karlson et al. (*Arthritis Rheum.*)	2003	122 (SLE)	12 months	RCT	**Positive:** Psychoeducational intervention significantly improved physical function.
Evers et al. (*J. Psychosom. Res.*)	2003	78 (RA)	5 years	Prosp	**Positive:** Avoidance stress-coping and decreased social support predicted the exacerbation of RA.
Buljevac et al. (*BMJ*)	2003	73 (MS)	1.4 years	Prosp	**Positive:** Stressful events predicted the exacerbation of MS.
Mohr et al. (*Neurology*)	2000	36 (MS)	25 months	Prosp	**Positive:** Life events were significantly associated with abnormal findings detected by MRI.
Multon et al. (*Arthritis Rheum.*)	2001	31 (RA)	15 months	RCT	**Negative:** Psychotherapy did not attenuate RA symptoms.
Costa et al. (*Arthritis Care Res.*)	1999	42 (SLE)	8 months	Prosp	**Positive:** Life events predicted physical impairment induced by SLE.
Schwartz et al. (*Ann. Behav. Med.*)	1999	101 (MS)	6 years	Prosp	**Positive:** Life events were significantly associated with MS symptoms.

SLE=systemic lupus erythematosus; MS=multiple sclerosis; RA=rheumatoid arthritis; Prosp=prospective observation; RCT=randomized controlled trial.

(2). The effect of stress on allergic disease

Almost all the previously published studies have reported a causal link between stress and allergic diseases (Table 3). Interestingly, in one retrospective study conducted in Kobe, the atopic dermatitis of refugees under great psychological stress from a natural disaster, the Hanshin–Awaji Great Earthquake, became worse.

In order to investigate the effect of psychological stress in childhood on asthma in adults, we are now undertaking an experiment using a mouse model of asthma (not yet published). In this study, Balb/c mice at the age of 3 weeks were exposed to communication box-induced stress for 1 h per session at a frequency of three times a week. At the ages of 8 and 10 weeks, the mice were sensitized with ovalbumin (OVA), and at the age of 11 weeks their airways were challenged with OVA mist for 30 min per day for 3 consecutive days. The airway inflammation levels were assessed by the total number and subpopulation of mononuclear cells in the bronchoalveolar lavage. The results showed that psychological stress by the communication box at the age of 3 weeks significantly exacerbated airway inflammation at the age of 11 weeks. Furthermore, pretreatment with RU-486, a glucocorticoid receptor antagonist, before the administration of OVA almost completely eliminated stress-induced exacerbation of airway inflammation in the BAL mice. In addition, the stressed mice

Table 3
The effect of stress on allergic disease

Author (Journal)	Year	Sample (Disease)	Duration	Design	Result
Wright et al. (*Am. J. Respir. Crit. Care Med*)	2002	496 (Asthma)	14 months	Prosp	**Positive:** Caregiver's stress predicted an exacerbation of childhood asthma.
Sandberg et al. (*Acta Paediatr.*)	2002	90 (Asthma)	18 months	Prosp	**Positive:** Negative life event predicted an exacerbation of childhood asthma.
Huovinen et al. (*Allergy*)	2001	11,540 (Asthma)	15 years	Prosp	**Positive:** Extroversion was a risk factor for asthma in females.
Sandberg et al. (*Lancet*)	2000	90 (Asthma)	18 months	Prosp	**Positive:** Negative life event predicted an exacerbation of childhood asthma.
Kodama et al. (*J. Allergy Clin. Immunol.*)	1999	1457 (AD)	4–11 months	Retro	**Positive:** As refugees suffered increased distress from the Hanshin–Awagi Great Earthquake, their atopic dermatitis became worse.
Contance et al. (*Pediatric*)	1999	1528 (Asthma)	9 months	Prosp	**Positive:** Patient and caregiver psychosocial factors were associated with an increase in the morbidity of asthma.
Anderzén et al. (*J. Psychosom. Res.*)	1997	55 (AR)	12 months	Prosp	**Positive:** Stress induced by migration increased allergic reaction.
Gustafsson et al. (*J. Pediatr.*)	1994	100 (Asthma)	18 months	Prosp	**Positive:** Poor family relationship predicted an exacerbation of childhood asthma.
Lammintausta et al. (*Int. J. Dermatol.*)	1991	801 (AD)	12 months	Prosp	**Positive:** Psychological stress was found in one-half to two-thirds of the patients.

AD = atopic dermatitis; AR = allergic reaction; Prosp = prospective observation; Retro = retrospective study.

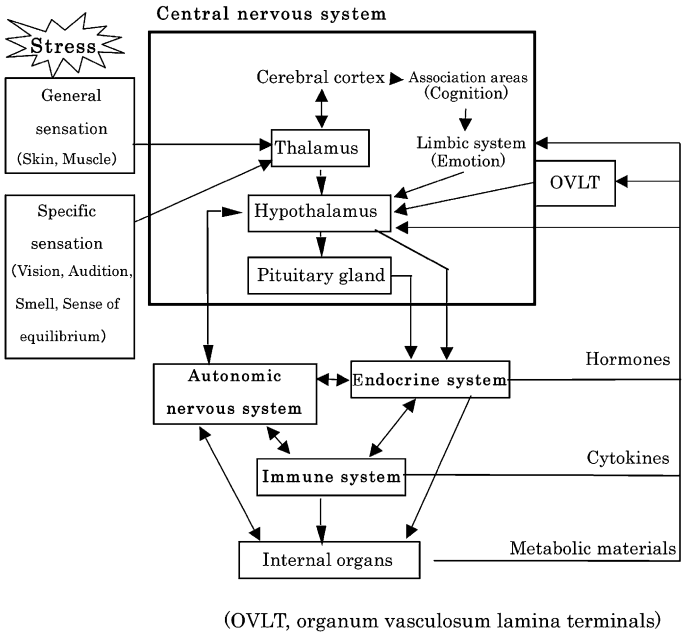

Fig. 2. The relationship between stress and the neuro–endocrine–immune systems.

exhibited a significant increase in blood glucocorticoids after the administration of OVA mist in comparison to the control mice. These findings indicate that hyporesponsiveness of the HPA axis mediates such stress-induced exacerbation of asthma.

6. Conclusions

To summarize, this review of the PNI of the mind and body, Fig. 2 shows the relationship between stress and the neuro–endocrine–immune system. Sensory stressors stimulate the hypothalamus, which in turn stimulates the cerebral cortex and associated areas, and the limbic system, a center of emotion, is thus stimulated. The limbic system and thalamus activate the hypothalamus, which is the center of the autonomic nervous and endocrine systems. Thereafter, these systems affect the immune system, which produces several cytokines. The internal organs are influenced by these three systems. Conversely, these hormones, cytokines and metabolic materials also affect the central nervous system. As shown here, when functioning normally, the response of these three systems to stress results in the maintenance of homeostasis of the organs.

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