

Review Article

Stress and asthma

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ABSTRACT

Three factors in recent medical research and treatment (advances in the field of psychoneuroimmunology, epidemiological evidence regarding important interaction between psychosocial factors and development of disease, and the recognition of the importance of patient education for self-management of asthma) have led clinicians and researchers to reconsider the role of psychosocial stress in asthma. There are many reports suggesting that stressful life events, family problems and a behavior pattern that increases psychological conflict may influence the development or relapse of asthma and influence its clinical course. Depression is known as one of the risk factors of fatal asthmatic attack. In laboratory studies, about 20% of asthmatics were considered reactors who showed an airway change after exposure to emotional stress. Studies regarding the pathway of stress effect on allergy and asthma are reviewed and discussed from the standpoint of psychoneuroimmunology; for example, the enhancement of IgE production and increased susceptibility to respiratory infection by stress, conditioned anaphylaxis and nerve/mast cell interaction, the effect of stress on various bronchial responses and the inhibition of the immediate and late asthmatic response by anterior hypothalamic lesioning.

Key words: asthma, brain immune interaction, conditioned histamine release, psychoneuroimmunology, stress.

INTRODUCTION

Although there have been many clinical, psychological and biological studies suggesting that stress and psychosocial factors may affect the incidence and symptomatology of asthma, their roles in the genesis remain controversial because the mechanisms are not well understood. Recent advances in the field of psychoneuroimmunology linking psychosocial stress, the central nervous system, and alteration in the immune and endocrine function, have provided possible biological pathways through which stress may influence the development and expression of asthma. Some epidemiological studies also have demonstrated an association between life stress, social support network, behavior pattern, and the development of diseases.

In addition to these, some guidelines for diagnosis and management of asthma emphasize the importance of education for self-management in asthma care, because the psychosocial factors such as family dysfunction or psychological distress may work as a risk factor of a fatal asthma attack and may influence health behaviors. These trends in medical research and care have led both clinician and researcher to reconsider the role of stress in asthma.

In the present paper, the studies regarding the effect and role of stress and psychosocial factors in the onset and exacerbation of asthma are reviewed. In the section on the pathway of stress effect on asthma, the possible mechanisms are discussed from the viewpoint of psychoneuroimmunology; for example, stress-induced enhancement of IgE production, stress-induced susceptibility to infection, conditioned histamine release and nerve/mast cell interaction or the brain immune interaction.

CLINICAL STUDY

Psychosocial factors in asthma

The basic feature of asthma is characterized by increased airway responsiveness, which may be related to chronic

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Received 12 July 1999.

eosinophilic inflammation and impaired neural control in the respiratory tract.¹⁻⁴

The airway obstruction may be caused by a number of factors, including infection, inhalation of cold air, exercise, exposure to allergens or irritants. On the other hand, it has been reported that psychosocial factors, including emotional or physical stress, may work as a direct trigger of bronchial obstruction or as a precipitating factor in the exacerbation of asthma.^{5,6} The consideration of psychosocial factors and psychotherapy is thought to be necessary to control asthma in some cases. The importance of the consideration of the psychosocial factors as well as pharmacotherapy and patient education is described in international consensus reports of diagnosis and management of asthma.⁷

It is well known that acute severe stress such as a disaster or war influences the occurrence or the clinical course of some diseases. The increase in the number of hospitalized patients with asthma as well as pneumonia, peptic ulcer or myocardial infarction immediately after the Hanshin-Awaji Earthquake has been reported.^{8,9} However, daily stress such as interpersonal or role conflict in the family or at the workplace, which is often accompanied by negative emotions, seems to be more important in clinical practice than acute severe stress.^{10,11}

Ago *et al.* reported that stressful psychosocial factors were found within 1 year before the onset of asthma in 91.8% of 209 asthmatics. These psychosocial factors were closely related to the life situation in each onset age.¹² For example, in childhood, separation from parents or psychological conflicts between parent and child; in the young and middle-aged, the role or interpersonal conflicts in the family or at the workplace; and in elderly persons, bereavement or retirement. They also reported the advantage of the stepwise psychosomatic treatment, which for intractable cases of asthma consists of pharmacotherapy and stepwise psychotherapy in five stages.¹³

The relationship between the four factors (i.e., stressful life events before the onset of asthma; behavior patterns, including coping; personality profiles and experience of difficulties in early life; and clinical course of asthma) was investigated. Regression analysis of the data from 74 adult asthmatics indicated that a heavy work-load, scrupulosity, compulsive personality and not seeking social supports, can be related to the severity of asthma, and that problem-solving behavior may contribute to the improvement of asthma.¹⁴ Although complete remission is sometimes observed in some cases with asthma, especially in adolescents, atopic disposition manifested

by IgE antibody level and relatively reduced bronchial hypersensitivity to aceptylcholone are still found in these cases.¹⁵ Even after a complete remission for several years, some persons suffer a relapse of asthma. Nagata investigated the relationship between stress and a relapse of asthma after more than 3 years of complete remission in a case-controlled study of three groups consisting of asthmatics with and without remission and controls. Asthmatics in relapse experienced significantly more stressful life events for 2 years before the relapse than controls during a corresponding term.¹⁶ De Araujo reported that the asthmatics who showed a high score for life change and a low ability for stress coping and social adaptation, needed a higher dose of prednisolone to control asthmatic symptoms.¹⁷

Family function is an important factor of health outcomes in general, and this has been shown to be the case for asthma as well. Family structure is also an important correlate of health outcomes. The relationship between severity of chronic diseases and maladjustment varies significantly within different family structures. Many of the psychosocial factors implicated in the rise in asthma morbidity and mortality are related to family structure.^{18,19}

Wright *et al.* reviewed the data from the Neighborhood Asthma Coalition (NAC), which showed that children of socially isolated parents had more frequent asthma symptoms, more days of activity limitation, poorer asthma management practices and more emergency department visits than those of non-isolated parents/caregivers.²⁰ Subsequent interventions conducted by NAC, which emphasizes neighborhood and community organization strategies and social support to help asthmatic families, have resulted in reductions in acute care for asthmatic children.

These results suggest that stressful life events, family dysfunction and a behavior pattern that increases psychological conflict may accelerate the onset or relapse of asthma and influence its clinical course, and that intervention may be effective for its control.

Depression and asthma

There are reports in the literature relating asthmatic death to depression.²¹⁻²³ Stunk *et al.*, in their study of factors that differentiated children who died of asthma from matched controls, emphasized the importance of psychosocial factors that included depression, poor self-care, disregard of asthma symptoms and interpersonal conflict.²² Miller reviewed the articles regarding fatal asthma,

especially those relating to the relationship between depression and its role in death from asthma.²³ He proposed the hypothesis that depression is associated with a shift towards increased peripheral and parasympathetic activity or cholinergic imbalance, leading to an exacerbation of pathophysiologic symptoms and culminating in sudden death from asthma.

Effect of stress and emotional arousal on pulmonary function in asthma

There are many clinical reports stating that an asthmatic attack is immediately preceded by emotional stress. Some laboratory trials using controlled stressors have been conducted to induce feelings such as anger, fear, anxiety and conflict, and the resulting changes in lung function evaluated. In these studies exposing the individual to trigger stimuli, mental arithmetic, hypnotic suggestion of cough, anger, fear of asthma attack and tape- or video-recorded anger-provoking or fear-provoking stimuli were used as emotional stressors. Isenberg *et al.* reported that in five such studies, 38 of 95 (40.6%) asthmatics showed airway change.²⁴

The most widely used method for assessing the effects of suggestion on airway function is that subjects inhale a substance that they believe to be a potent bronchoconstrictor, but is actually an inert substance such as saline. The effect of this manipulation on the airway function is then evaluated. Luparello *et al.* reported first that, when reacting to the suggestion, 19 of 40 severe asthmatics, but none of 40 non-asthmatic controls, showed more than a 20% decrease of conductance/thoracic gas volume (Gaw/TGV) measured by whole-body plethysmography.²⁵ Isenberg *et al.* calculated in their review article that of the percentage of changes occurring in individual subjects, 152 of the total group of 427 asthmatics (35.6%) in 20 studies were considered reactors by at least some criteria, but because of methodological considerations, the percentage might be conservatively estimated as closer to 20%.²⁴

Direct evidence for parasympathetic involvement in suggested airway constriction has been obtained from studies using parasympathetic blocking agents. McFadden *et al.* found that intravenously injected atropine blocks the suggestion effect.²⁶ Neild and Cameron also found that inhaled ipratropium bromide (parasympathetic blocking agent) abolishes the suggested airway constriction.²⁷ The vagal mediation hypothesis was consistent in preliminary studies. However, a systematic study of the hypothesis has

yet to be undertaken, because a parasympathetic blocking agent by itself has bronchodilative effects.

PATHWAY OF STRESS EFFECT ON ALLERGY AND ASTHMA

Stress and allergic reaction

Persoons *et al.* reported that acute emotional stress using electric foot-shock and subsequent intratracheal administration of trinitrophenyl (TNP)-conjugated keyhole limpet hemocyanin to rats resulted in a dramatic increment of TNP-specific immunoglobulin isotype concentrations in serum, including IgE.²⁸ They advocated the view that acute emotional stress can contribute to the onset or severity of allergic asthma by lowering the threshold of induction of aeroantigen-specific IgE production in the lung. In contrast to this study, Fukui *et al.* reported that restraint stress for 12 h before the ovalbumin sensitization suppressed the IgE, IgG and IgG2 antibodies, and interleukin (IL)-2, IL-4 production in mouse.²⁹ There are many reports suggesting that both acute or chronic stress affects humoral and cellular immunity; however, the effect of stress on the immune system may be different with the severity and type of stressor, and also the timing of exposure to stress at the stage of antibody production and cellular immunity.^{30,31}

In a study on humans, Bernton *et al.* reported the suppression of delayed-type hypersensitivity response to seven antigens and tumor necrosis factor (TNF)- α secretion by monocytes, with an increase in circulating IgE at 4 and 6 or 8 weeks during 8 weeks of extremely stressful military training, which suggests that there is a decrease in the production of the macrophage-activating factor gamma-interferon and an increase in IL-4 and IL-5 production at tissue level.³² These changes suggest the activation of T helper cells expressing the Th2-like phenotype and the suppression of T cells expressing the Th1-like phenotype. They hypothesized that T helper cell responses of the stressed trainees shifted from a Th1 to a Th2 pattern due to hypercortisolemia, because cortisol was found to increase IgE synthesis in response to IL-4 and to suppress IL-1 and TNF production by monocytes in an *in vitro* study.

In addition to these studies, there is evidence that parental stress is associated with subsequent onset of wheezing in children between birth and 1 year.³³ It has been speculated that stress triggers hormones that may influence Th2 cell predominance, perhaps through a

direct influence of stress hormones on the production of cytokines that are thought to modulate the direction of lymphocyte differentiation.

There are some reports regarding the relationship between stress and bronchial reaction in animals. An enhancement of bronchial reaction to ovalbumin (OA) antigen inhalation after a 16 h restraint was reported in passively sensitized guinea-pigs with anti-OA IgE antibody 7 days before. In this study,³⁴ the bronchial reaction was monitored using the index of oxidized hemoglobin in the tissue (Iso₂), which closely correlates with respiratory resistance; the reaction was significantly more enhanced in the stress group than in the control group. Eight of 12 guinea-pigs in the stress group, in contrast to two of 12 guinea-pigs in the control group showed fatal bronchial reactions. Iwasaki *et al.* observed a decrease of peripheral eosinophils, an increase of eosinophils and radical oxygen production in the bronchoalveolar lavage fluid (BALF), and an increased bronchial responsiveness in *in vivo* and *in vitro* studies of restraint-stress guinea-pigs.³⁵ Chihara *et al.* reported an increase of eosinophil and leukocyte-adhesion to plasma-coated glass, and leukocytes to autologous bronchial ciliary cells in electrically foot-shocked guinea-pigs. They speculated that stress might be involved in adhesion-molecule expression resulting in acceleration of allergic inflammations such as bronchial asthma.³⁶ Thus, animal studies suggest that stress may influence the bronchial reactions.

Respiratory infection and asthma

Respiratory infection, which is the most common trigger of asthmatic attacks, is often observed before the onset or exacerbation of asthma.^{37–39} Several studies have demonstrated an impact of life stress on basal immune status, which in turn brought about a dysregulation of the immune system and altered the vulnerability of the individual.^{40–42} Cohen *et al.* reported that a psychological-stress index composed of negative life events, perceived stress and negative affective measures was associated with susceptibility to a biologically verified clinical cold among 394 adults who had been exposed to five different upper respiratory viruses.⁴³ Kiecolt-Glaser *et al.* showed that down-regulation of the immune response to influenza virus vaccination is associated with a chronic stressor (caregiving) in the elderly.⁴⁴ Stress can alter the immune response to a latent virus in humans, including alterations in the cellular immune system in response to latent Epstein–Barr virus (EBV) and Herpes

simplex virus, and can cause decreased memory response to viral-specific proteins and stress-associated decreases in the EBV-specific cytotoxic T cell function.^{42–45} Sheridan *et al.* demonstrated that both the hypothalamic–pituitary–adrenal (HPA) axis and the central nervous system (CNS) were operative in stress-induced suppression of antiviral immunity and modulation of viral pathogenesis.⁴⁶ They found that restraint-induced stress elevated glucocorticoid and catecholamine levels, depressed lymphadenopathy, reduced mononuclear infiltration in the lung, suppressed virus-specific cytotoxic and lymphokine-mediated T cell responses, and enhanced the pathogenesis of experimental viral infections in mice.

These studies suggest that stress-induced immunosuppression and increased susceptibility to respiratory infection may be factors that influence the onset or exacerbation of asthma and provide us with a possible causal mechanism in the stress-asthma paradigm.

Conditioned histamine release and nerve/mast cell interaction

There have been many anecdotal reports of associative learning in allergic reactions or conditioned asthma attack.^{47,48} For example, it was reported in the 19th century that an asthmatic woman who had an allergic reaction to roses experienced an attack when exposed to an artificial rose.⁴⁹ In recent studies in Japan about 20 to 40% of asthmatics stated that their asthma attacks may have been induced by a specific situation, such as before stressful events or awareness of not having taken any medicine.⁵⁰ The number of persons who had these experiences was relatively higher among females or severe asthmatic patients than among males or mild cases of asthma.

Several studies have suggested that anaphylaxis can occur in the absence of any antigenic or physical stimulus and may represent a conditioned response.^{47,51–53} Conditioned stimuli such as odor or sound may become associated with antigens in such a way that subsequent exposure to these stimuli will elicit anaphylactic responses. The antigen provocation is an unconditioned stimulus that elicits anaphylaxis, an unconditioned response.

Russell *et al.* reported that after a classic conditioning procedure in which an immunologic challenge was paired with presentation of an odor, guinea-pigs sensitized by intracutaneous bovine serum albumin (BSA) showed a plasma histamine increase at the same level as that after an antigen inhalation challenge when presented with the

odor alone.⁵¹ Okada *et al.* demonstrated conditioned histamine release after a conditioning process with dimethylsulfide (DMS) (sulfur smelling) and OA inhalation in sensitized guinea-pigs with inhaled ovalbumin (OA).⁵² They observed that conditioned histamine release was inhibited by substance P (SP) antagonist.

MacQueen *et al.* reported conditioned release of mast cell-specific mediator, rat mucosal mast cell protease (MRCP) II, which is found only in the thymus-dependent mast cell in the mucous lamina propria of the intestine and lung. They found that there was significantly more protease release after the audiovisual cue in the rats that were injected with OA paired with an audiovisual cue than in the rats that had received the cue and the antigen in a non-conditioning manner.⁵³ In a human study, Gauci *et al.* reported the Pavlovian conditioning of nasal tryptase release in a subject with allergic rhinitis.⁵⁴ These reports support a role for the central nervous system as a functional effector of mast cell function in the allergic state.

According to progress in neurochemistry, it has become clear that various neuropeptides can cause histamine release from mast cells and sensory nerves closely associated with mast cells in rats, mice and humans.⁵⁵⁻⁵⁷ SP and calcitonin gene-related peptide (CGRP), both of which can cause mast cell degradation, are found abundantly in sensory nerve terminals in rodents.^{58,59} It is also known that mast cells, as well as SP, are involved in the axon reflex responsible for the flare reaction to noxious stimuli, and that antidromic nerve stimulation can cause neurogenic edema, mast cell degradation and augmentation of histamine release.⁶⁰⁻⁶²

Barnes provided the hypothesis, 'axon reflex theory', that the neurogenic inflammation at the airway caused by these sensory neuropeptides may play an important role in increasing airway hypersensitivity observed in asthmatics.⁶³ Bienenstock and Tomioka, by means of immunohistochemical methods and the electron microscope, found that between 67 and 87% of all mast cells in the intestinal lamina propria of rats infected with *Nippostrongylus brasiliensis* were touching nerves, and that these membrane contacts were between subepithelial mast cells and non-myelinated nerve (c-fiber) containing SP, CGRP and neuron-specific enolase.⁶⁴ There is increasing evidence regarding the interaction between sensory nerves and mast cells. It is thought that the cytokines such as IL-1, IL-3, IL-5, IL-6 produced from an activated T cell and fibroblast enhance proliferation of mast cells, and a substance like nerve growth factor

(NGF) released from mast cells promotes growth of the sensory neurons and makes a tight junction between mast cells and nerve fibers.⁶⁵

These studies suggest that conditioned histamine release may occur through the stimulation of the mucous mast cells by sensory neuropeptides. Even though these results do not provide conclusive evidence, there is considerable evidence *in vitro* and *in vivo* to support both morphological and functional nerve/mast cell interactions. Recently, Clark and Squire reported the importance of awareness of classic conditioning.⁶⁶

The onset mechanisms of the asthma or allergic symptoms induced by suggestion or conditioning observed in clinical practice are still somewhat unknown, but the study regarding functional and morphological nerve/mast cell interaction provides an important key to understanding them. The next step in the study of Pavlovian conditioning of anaphylaxis will be an investigation of the route of the transmission of stimulus and the interaction between the central nervous system and sensory neuropeptide release.

Effect of central nervous system on the bronchial reaction

The hypothalamus is known as the control center of the endocrine and autonomic nervous systems. Recent studies suggest that the hypothalamus may play an important role in the immuno-allergic response. There are also some reports stating that anterior hypothalamic lesion (AHL) decreases the lethal anaphylaxis and suppresses the circulatory antibody, lymphocyte response to phytohemagglutinin (PHA) mitogen and natural killer (NK) activity in rats and mice.⁶⁷⁻⁶⁹

The effect of anterior hypothalamic lesions on both immediate and late asthmatic responses has been investigated. Passively sensitized guinea-pigs with 1600 titers of anti-OA IgE antibody 7 days before the antigen challenge, were used for the model of immediate asthmatic response. The bronchial reaction of unanesthetized guinea-pigs was monitored continuously, using the index of oxidized hemoglobin in the tissue (Iso₂) on the sides of their feet. The decrease of Iso₂ after the histamine and OA antigen inhalation in the unilateral and bilateral anterior hypothalamic lesion groups was significantly less than that of the sham operation group.³⁴ This result suggests that AHL may suppress the bronchial reaction in a non-specific manner. The late asthmatic response model of Brown Norway (BN) rats was used to investigate the

effect of AHL on bronchial reaction.⁷⁰ Bilateral lesions in the medial preoptic area (MPO) in the hypothalamus were produced by a micro-injection of 50 nL of 0.3% kainic acid. The late asthmatic response indicated by eosinophil counts in BALF and the peribronchial area in the lung was significantly lower in AHL groups than in the sham operation groups.⁷¹ The mechanism of the decrease of allergic reaction by AHL may be due to the destruction of the parasympathetic center, which may produce an imbalance in the autonomic nervous system, resulting in increased sympathetic activity and concomitant elevated cyclic AMP (cAMP) levels. Increased cAMP suppress the contraction of bronchial smooth muscle and the functioning of mature lymphocytes such as antibodies and cytokine production, which is in accordance with the inhibitory effect of AHL on lymphocyte and bronchial reaction.

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