Stress and Immune Function

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Abstract: In the presence of internal and external stress, homeostasis of the internal environment of the body is maintained through the regulatory functions of the nervous, endocrine and immune systems. These three systems, sharing an information transmitting mechanism, function as an integrated regulatory system of the body. The information-transmitting factors include hormones, cytokines, and neurotransmitters. Stress influences the immune system through two routes, the hypothalamus-pituitary-adrenal axis and the autonomic nervous system. The response to the immune system through these pathways differs according to stress type, amount, and duration, and the condition of the body receiving the stress. Clinical and basic research will be reviewed to show the influences of stress on the immune system.

Key words: Stress; Immune function; Hormone; Neurotransmitter; Homeostasis

Introduction

In the presence of internal and external stress, homeostasis of the body’s internal environment is maintained through the regulatory functions of the nervous, endocrine and immune systems. These three systems, sharing an information-transmitting mechanism, function as an integrated regulatory system of the body. The information-transmitting factors include hormones, cytokines, and neurotransmitters.

Stress affects the immune system through two pathways, the hypothalamus-pituitary-adrenal axis and the autonomic nervous system. The response of the immune system through these pathways differs according to the type, amount, and duration of stress and the condition of the organism subjected to stress. Also, the extent to which the endocrine and nervous systems modulate the response of the immune system to stress differs according to the type of target immune system.

Clinical Studies

In various circumstances where individuals experience worry, grief or depression, the rate of infectious diseases, allergic diseases, autoimmune diseases, and cancer has been reported to increase.

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Bartrop et al. reported that the immune response of bereaved spouses decreased within 2–8 weeks after the death of their mates.1) Schleifer et al. reported a significant reduction of lymphocyte blastogenesis capability in men after the death of their wives from breast cancer.2)

In addition, the suppression of PHA response (proliferation of phytohemagglutinin) of lymphocytes in peripheral blood, reduced production of interferon, and reduced activity of NK cells3,4) during stress tests have been reported.

An epidemiological study by Cohen et al. reported the occurrence of respiratory infections, viral isolation, and increased antibody levels when rhinovirus, a causal virus of the common cold, was dropped into the noses of healthy subjects.5) They found that the susceptibility to viral infection differs according to the subjective intensity of stress.

It has recently been reported that depression is partly responsible for cancer because of reduced immune function.6) In patients with depression, a reduction in lymphocyte blastogenesis capability in peripheral blood in response to mitogen (activity promoting mitoses of lymphocyte) was observed, and it was found that the more severe the depression, the lower the blastogenesis response.

Additionally, a reduction in the number and activity of NK cells was reported in depression. This finding can be attributed to the acceleration of the hypothalamus-pituitary-adrenal axis.

Thus, it has been shown that mental condition significantly influences the immune function. In humans, the response differs according to the personality and physical factors of the person under stress. Table 1 summarizes the major reports on stress and suppressed immune function.

**Basic Studies**

Many basic studies have been conducted using animal models. Reduction in the activity of NK cells in response to low- or high-temperature stress has been reported in rats. It has also been reported that lymphocyte blastogenesis in response to mitogen is suppressed in mice in response to short-term exposure to noise. However, it was also reported that immune function is sometimes enhanced by short-term fasting or pain stimulation.7)

The effect on immune response depends on

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Table 1 Suppression of Immune Function by Stress

<table>
<thead>
<tr>
<th>Types of stressors</th>
<th>Immune function</th>
<th>Published</th>
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</thead>
<tbody>
<tr>
<td>Mental and social stress</td>
<td>Increased morbidity rate by upper bronchial infection</td>
<td>1962, Jacob</td>
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<tr>
<td>Chronic daily stress</td>
<td>Reduced resistance to streptococcal infection</td>
<td>1962, Meyer</td>
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<tr>
<td>Sleep disorder</td>
<td>Reduced phagocytic capacity against streptococcus, reduced production of interferon</td>
<td>1976, Palmblad</td>
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<tr>
<td>Death of a spouse</td>
<td>Reduced T cell function</td>
<td>1977, Bartrop</td>
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<tr>
<td>Effect of stress due to changes in life</td>
<td>Reduced cytotoxic function</td>
<td>1978, Green</td>
</tr>
<tr>
<td>Certification examination</td>
<td>Reduced lymphocyte PHA response</td>
<td>1982, Dorlan</td>
</tr>
<tr>
<td>Worry or depression with changes in life</td>
<td>Reduced NK cell activity</td>
<td>1983, Gottschalk</td>
</tr>
<tr>
<td>Depression</td>
<td>Reduced lymphocyte response</td>
<td>1986, Kronfol</td>
</tr>
<tr>
<td>Death of a spouse</td>
<td>Reduced lymphocyte PHA and PWM response</td>
<td>1983, Schleifer</td>
</tr>
<tr>
<td>The elderly without social support</td>
<td>Reduced lymphocyte PHA response</td>
<td>1985, Thomas</td>
</tr>
<tr>
<td>Mental stress</td>
<td>Increased morbidity rate from common colds</td>
<td>1991, Cohen</td>
</tr>
<tr>
<td>Loss experience, interpersonal stress</td>
<td>Increased herpes labialis recurrence</td>
<td>1991, Schmidt</td>
</tr>
<tr>
<td>Natural disaster (hurricane)</td>
<td>Reduced NK cell activity</td>
<td>1997, Ironson</td>
</tr>
</tbody>
</table>

PHA: phytohemagglutinin  PWM: pokeweed mitogen
individual ability to control stress. When rats or mice were given uncontrollable electroshocks, blastogenesis PHA and Con A lymphocyte response and NK cell activity were reduced. In contrast, when electroshock was self-controllable, the immune responses were not suppressed even when the same voltage was administered.

In addition, the authors investigated the relationship between restraint stress and immune function in mice.

A study of the number and subsets of cells in the organs of mice under restraint stress reported that the ratio of CD4, CD8, and B cells in the spleen and mesenteric lymph nodes remained the same, but that the number of cells was significantly decreased at 12-hours and recovered to the original level within 24 hours. Under the restraint stress, a decrease of lymphocytes was observed in organs such as the thymus and liver, while the ratio of lymphocyte subsets and the number of cells such as CD4, CD8, and B cells was increased in bone marrow.

The effect of 12-hour restraint stress on antibody production was found a reduction of IgE, IgG 1, and IgG 2a antibodies in blood collected over time from mice immunized with OVA.

The effect of stress on the immune system differs depending on the type, amount, duration of the stress, and the condition of the individual subjected to stress.

Correlation between Stress and the Nervous, Endocrine and Immune Systems

Stress affects the central nerve system through sensory systems, such as auditory and visual, and then it affects the immune system through the hypothalamus-pituitary-adrenal axis or the autonomic nervous system.

1. Stress and the endocrine and immune systems

Emotional stress activates CRH (corticotropin-releasing hormone) neurons in the nucleus paraventricularis of the hypothalamus by stimulating the limbic system, especially the amygdaloid nucleus, causing the hypothalamus to secrete ACTH (adrenocorticotropic hormone), after which the adrenals are stimulated to secrete glucocorticoids.

On the other hand, the hippocampus exerts a suppressive action on the CRH neurons. The CRH neurons send fibers to POMC (pro-opiomelanocortin) neurons of the arcuate nuclei, which allows stimulation and secretion of β-endorphins, α-MSH (α-melanocyte-stimulating hormone), and ACTH, leading to the modulation of various immune functions. β-endorphin and ACTH are antagonists to the secretion of CRH from the paraventricularis.

Generally speaking, increased glucocorticoid binding to the receptors of the hippocampus antagonizes the secretion of CRH through the paraventricularis under acute stress. In contrast, glucocorticoidemia downregulates the receptors of the hippocampus, attenuating the antagonistic response, and glucocorticoidemia persists under chronic stress. Decreased lymphocytes and eosinophils in blood and increased excretion of 17KS (an intermediate sex steroid) and 17OHCS (a glucocorticoid indicators) in urine are observed under stress.

Adrenocortical hormones such as glucocorticoids have anti-inflammatory, immunosuppressive, and anti-tumor actions. Glucocorticoid receptors are found in almost all cells except for erythrocytes. The antagonist action of glucocorticoids on the immune system is expressed directly or indirectly by suppressing mediators.

Moreover, growth hormones, gonadotropin, and prolactin are susceptible to stress. Those hormones are known to affect the immune system.

2. Stress and the nervous and immune systems

The nervous system transmits external stimulation received by receptors through the neu-
rons, and responds to external changes through effectors. Additionally, a part of the nervous system, the autonomic nervous system, maintains homeostasis of the internal environment. Organs are regulated by the functions of the sympathetic and parasympathetic nerves. The immune tissue also has many autonomic nerves. The core of the autonomic nervous system is found in the hypothalamus, and it has been shown that the core of emotion is also in the hypothalamus and the limbic system. Emotion also influences immune function through autonomic nerves. Immune tissues such as the thymus, bone marrow, spleen, and lymph nodes are controlled by both sympathetic and parasympathetic nerves.

The autonomic nervous system regulates not only microcirculation of lymphatic tissue through vessels, but also controls lymphocytes directly, through the action of nerve fibers extending to the parenchyma which is full of lymphocytes. T and B lymphocytes have α- and β-adrenoceptors through which immune response is modulated by the autonomic nervous system. Stimulated α-receptors promote immune responses by reducing intracellular cAMP, while stimulated β-receptors suppress lymphocyte function by increasing intracellular cAMP.

Under stress, β-endorphin is excreted from the anterior hypothalamus and enkephalins from the adrenal medulla. Weigent et al. reported that receptors specific to nerve peptides were found on immunocytes. They include VIP (vasoactive intestinal polypeptides), substance P, catecholamines, and acetylcholine.

Those neurotransmitters modulate cell function by activating secondary messengers such as cAMP and cGMP through specific receptors. In addition, the neurotransmitters affecting the production of cytokines and physiological activity modulate indirectly immune responses.

The nucleus of the solitary tract, the core of the sympathetic nerves in the brainstem, sends noradrenergic fibers to sites full of CRH cells in the internal nucleus paraventricularis. The cerebellus nucleus has similar fibers connected to the nucleus periventricularis and the cerebral cortex which have thyrotropin-releasing hormone, somatostatin, and dopamine-containing cells.

Both nervous nuclei stimulate CRH secretion from the nucleus paraventricularis in parallel, forming a network with splanchnic nerve stimulation such as bleeding, and somatosenory stimulation such as pain. Thus, there is an interaction between the CRH secreted in the hypothalamus and in the sympathetic nerves.

**Conclusion**

Stress affects mental condition through the sensory system (nervous system) and the nonsensory system (immune system). Mental condition stimulates a homeostasis triangle: the nervous, endocrine, and immune systems.

In brief, emotions such as worry, depression, anger, grief, and pleasure induced by stress affect the immune system through nerves and endocrine system. Further investigation of the relationships between emotions and immune function from molecular-biological standpoint is essential.

**REFERENCES**

7) Fujiwara, R, and Orita, K.: The enhancement

