

Applied Bioregulation in Neuroendocrine Disease

Chronic Stress

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Chronic stress is often a reaction to the stimuli of a more or less hostile environment, to which most people living in the 21st century have succumbed. With increasing clarity, chronic stress is shown to be a causative agent of numerous diseases, especially those of neuroendocrine origin. A new cross-functional medical specialization is appearing, propelled by increasingly detailed knowledge about the biological foundations of the relationship between stress and a variety of diseases: psychoneuro-immunology.

The history of medicine has been a constant struggle between monism and dualism, between those researchers who consider the human being to be a unit and those who see in the individual the confluence of 2 separate entities: physical and spiritual, material and immaterial, metabolism and emotions, body and soul.

If we go back some 2,600 years, Hippocrates had already declared that health was a state inherent to the individual, whom nature had endowed with self-healing abilities. Furthermore, while a person lived in harmony with nature, his or her health would be maintained or, were it lost, could easily be recovered. Disease was only an imbalance resulting from a failure to observe the rules of Hygeia. Thus, the physi-

cian's mission would be to help individuals recover the lost equilibrium and teach them to live in accordance with the laws of nature (*vis medicatrix naturae*).

In contrast, students of the school of Aesculapius believed that for every disease there was a determined cause, a separate treatment, and some organs or systems involved, and that the most prestigious physician was the one who made the diagnosis and prescribed the correct treatment. This compartmentalized and highly specialized vision is that which now dominates "modern" medicine, one in which the idea of the individual is, incorrectly, not considered to be an indivisible entity, a single unit with one material component and another apparently immaterial component.

Fortunately, in the second half of the 20th century, the development of that highly specialized and fragmented medicine, with an impressive ability to delve into the core of the most subtle physiological processes, converged with the other, more humanist medicine descended from Hippocrates, which pays attention to the psycho-emotional aspects of humankind. We could say that the more cartesian-reductionist and more fiercely material medicine has discovered the influence of the human soul on physiopathological processes.

It is, therefore, absolutely fascinating that more than 2,000 years ago, the pineal gland was described by Galen, who credited it with the ability to regulate the flow of thought; in the 17th century, it was described by Descartes as the seat of the rational soul. What is surprising is the insight, from ancient times, that this area would be the gateway between body and soul and the approximation of what was being described to what we know today about the interrelationships between emotions and their physical responses.

The study of the relationships between mind and body has been termed psychoneuroimmunology, and what we are truly faced with is the most refined, holistic concept of medical science.

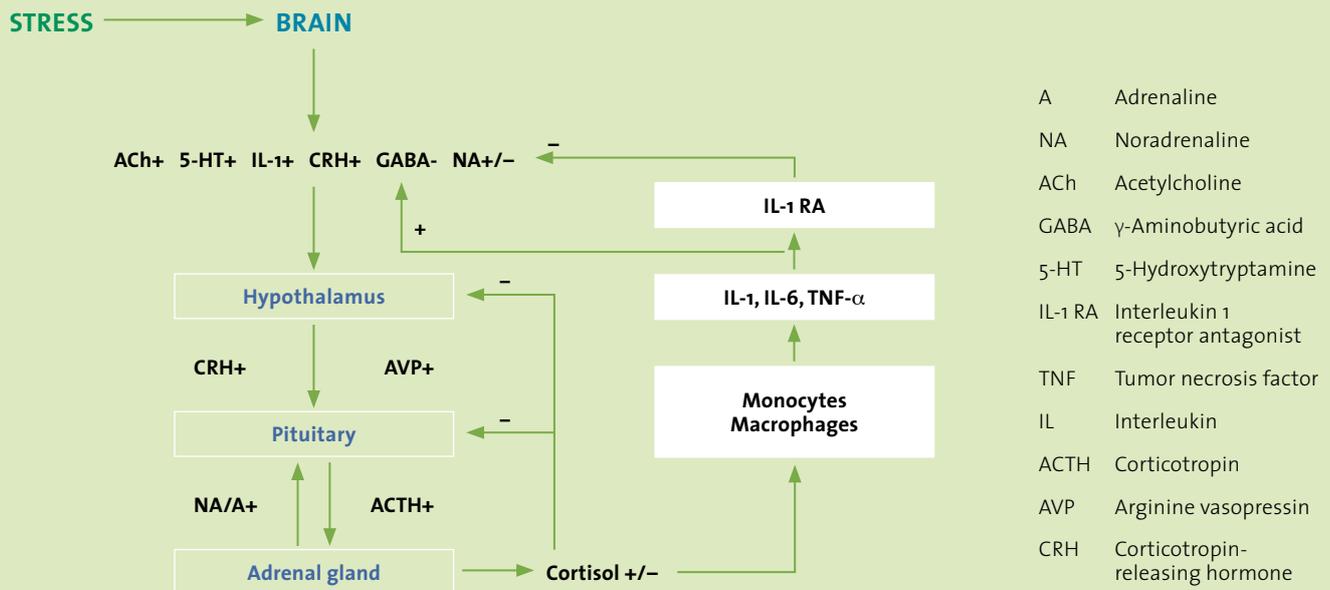


Figure 1: Relationship between the cortex, hypothalamus, pituitary gland, and adrenal glands (after Lack and Wright¹)

The hypothalamic-pituitary-adrenal system

The stimuli generated in the cerebral cortex by adverse situations such as stress or various pathological mental processes will create a response in the limbic system that triggers the release of several neurotransmitters (e.g., acetylcholine, 5-hydroxytryptamine, interleukin [IL] 1, corticotropin-releasing hormone [CRH], γ-aminobutyric acid [GABA], and noradrenaline). These neurotransmitters will ultimately activate the hypothalamic-pituitary-adrenal axis according to the cascade described later (Figure 1).

Corticotropin-releasing hormone and arginine vasopressin (AVP) are produced in the paraventricular nuclei of the hypothalamus. These substances are carried to the anterior pituitary gland, where they regulate the secretion of adrenocorticotropic hormone (ACTH or corticotropin). Adrenocorticotropic hormone travels through the bloodstream to the cortex of the adrenal glands, where

it stimulates the synthesis and release of glucocorticoids (GCs).

In turn, these GCs exert a negative feedback on several targets, including the adrenal cortex, inhibiting their own secretion; the pituitary gland, inhibiting ACTH production; and even the hypothalamus itself, down-regulating the release of ACTH and AVP. Glucocorticoids also act on the hypothalamus through the production of GABA, which ultimately inhibits this organ's synthesis of CRH and AVP. Another intermediate feedback regulator of the release of CRH in this process would be the one exerted on the noradrenergic and serotonergic neurons.²

Finally, we must not forget that the brain will also exert an influence on the sympathetic and endocrine system by means of the CRH that regulates the sympathetic nervous system. This has nerve endings in the bone marrow, thymus, and spleen, which are the cell factories responsible for cellular and humoral immunity.

The psychoneuro-immunology of stress

It is now clear that CRH plays a fundamental role in the response to stress. Administration of CRH produces a broad suppression of immune functions similar to that observed in depression or chronic stress.

Corticotropin-releasing hormone regulates immune functions through a central pathway and a peripheral pathway. By means of the central pathway, it notably suppresses the proliferation of lymphocytes and phagocytosis by neutrophils while increasing the number of neutrophils and cellular aggregation. It also decreases the quantity and activity of natural killer (NK) cells and IgG levels. In the peripheral pathway, its activity is based on the CRH receptors that exist on macrophages, monocytes, and helper lymphocytes. Corticotropin-releasing hormone reduces the replication and survival of spleen cells while simultaneously encouraging the migration of monocytes.

We have already seen how stress activates the production of CRH directly in the hypothalamus and indirectly through noradrenergic and serotonergic neurons. However, it also activates the autonomic nervous system. For these tasks, mediation by intermediaries such as acetylcholine, IL-1, and serotonin is required. Meanwhile, to balance this reaction, stress-inhibiting substances are also present, such as GABA; opioid peptides, whose producing neurons are closely related to CRH-producing neurons to establish an equilibrium; and a third group (e.g., adrenaline/noradrenaline) that acts on various senses.

With respect to the sympathetic nervous system, we could say that in states of stress it will be activated by CRH, and on being stimulated, it will produce adrenaline and noradrenaline. Peripherally, these substances will trigger a series of actions, such as an increase in blood pressure, blood glucose, heart rate, alertness, and vigilance, and inhibit the sensation of hunger and growth through the suppression of growth hormone (GH).

Stress affects various vital areas

The immune system

According to recent studies, the role of cortisol in the inhibition of the immune system appears to consist of suppressing the ability of immune cells to activate their own telomerase to reproduce their telomeres each time the cell divides. The telomere would, therefore, be shortened, a characteristic observed in pathological conditions, such as human immunodeficiency virus infection, osteoporosis, coronary heart disease, and even aging.³

Cancerous diseases

Stress significantly reduces the activity of NK cells.⁴ In laboratory experiments on animals subjected to stress, the rate of pulmonary metastases from induced breast cancers doubled.

Studies of women who underwent surgery for carcinoma of the breast have also shown a significantly reduced NK cell count in patients with high stress levels compared with those who controlled their stress, resulting from uncertainty about the treatment or prognosis of their disease.⁵

Infectious diseases

In laboratory experiments on animals subjected to stress conditions, their response to the flu virus decreased significantly. Along with high levels of plasma corticosterone, a decrease in the mononuclear cell population and a 60% to 95% decrease in IL-2 production in lymphoid organs were observed.

In preschool-aged children subjected to various situations of environmental stress, several changes in the CD4, CD8, and NK cell counts were observed, which have been correlated with respiratory diseases.⁴

Another experiment conducted on astronauts found that during periods of stress, there was a decrease in antibodies to the Epstein-Barr virus nuclear antigens, along with an increase in adrenaline and noradrenaline in the urine and a decrease in virus-specific T lymphocytes. This led to the reactivation of the Epstein-Barr virus in 11 of 28 astronauts.⁶

Wound healing

There also appears to be evidence from *in vitro* studies showing that fibroblasts would be less effective in matrix repair for recovery from inju-

ries and wounds in situations of psychological stress, precisely because of the presence of high tissue levels of corticosteroids. In one study of student volunteers who underwent small incisions on mucous membranes, the healing time was 40% longer during examination periods than during vacation periods. This longer duration was associated with a 30% decrease in IL-1 levels during examination periods.⁷

Stress and allergies

In a joint experiment, physicians and psychologists studied the relationship between stressful situations and an increase in the most common signs of allergies (rhinitis, sneezing, coughing, and conjunctivitis), along with the peculiarity that the allergic symptoms worsened in the following days while the stress stimulus continued. Analytically, this translates to a significant increase in IL-6 and catecholamines in the blood of stressed patients with symptoms of allergies.

There is another mediator, vasoactive intestinal polypeptide, that has been found in increased quantities in children who have experienced significant stress (typically parental separation) and that is closely linked to sensitization and the onset of allergic phenomena.⁹

In another recent experiment performed in Canada,¹⁰ it was found that maternal stress in the first 7 years of the child's life has a significant influence on the rates of childhood asthma because mothers in this situation are less likely to interact with and show affection to their children. This is recognized by the child's immune system, which could be considered an "affective" transmission of stress.

Systemic lupus erythematosus, depression, and stress

Distinct immunological changes have been found in patients with depressive syndromes of various degrees and clinical manifestations.¹¹ In contrast to healthy control subjects, an increase in B lymphocytes, antinuclear antibodies, and serum immunoglobulins can be observed in patients with depressive syndromes. Thus, depressive illnesses can demonstrate a certain relationship to autoimmunity. Also, many autoimmune diseases are characterized by major episodes of depression, especially systemic lupus erythematosus, regardless of treatment with GCs.

With depression in general, prolonged activity in the adrenal cortex is a factor that makes recovery notably difficult. These are patients in whom the administration of corticosteroids does not exert a negative feedback on their own cortisol levels.¹²

Growth and stress

As previously mentioned, sustained stress causes high levels of CRH, which in turn inhibits GH and insulinlike growth factor 1. The circulating corticosteroids also exert a negative feedback on GH production by the pituitary gland.²

Stress and sleep

Patients experiencing stress have a poor quality of sleep as a cause and a result of stress.^{5,13} Failure to follow circadian rhythms due to a lack of sleep reduces the amount of melatonin in the blood to below required levels. It is, therefore, presumed that its antioxidant activity cannot be performed. Also, melatonin's likely activity of promoting immunity by inhibiting the production of gonadotropins is inhibited.^{1,14}

Bioregulatory approach to stress

A fascinating opportunity remains open for bioregulatory medicine to establish treatment protocols consisting of immune regulatory medicines (e.g., Echinacea compositum and Engystol), medicines supporting brain function (e.g., Cerebrum compositum, Thalamus compositum, Ypsiloheel, Neuro-Injeel, Tonico-Injeel, Nervoheel, and Ignatia-Homaccord), and the classic organoregulators, such as Ovarium compositum, Pulsatilla compositum, Coenzyme compositum, Hepar compositum, Testis compositum, Thyreoidea compositum, Galium-Heel, and Ubichinon compositum. Neurexan, a medication for nervousness and insomnia, has recently been shown in preliminary studies to be possibly useful in anticipatory anxiety.¹⁵ ■

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