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REVIEW ARTICLES

The Neurochemistry of Stress: the Chemistry of the Stress Response and Stress Vulnerability

N. V. Gulyaeva[1]

Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia

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Abstract—Stress, which is an adaptive response of the body, is controlled by the brain. The neuroendocrine system, in particular the hypothalamo–pituitary–adrenal axis (HPAA), is a key player in the stress response. A number of studies have confirmed an association between stress and neurodegenerative and mental diseases and the major role of HPAA dysfunction and cortisol excess in this association. Although many signaling pathways stimulated by HPAA have been discovered, there are many possibilities for switching between these signal transduction pathways and for combining them; numerous factors would determine the involvement of definite mechanisms in the stress response. An aberrant neurochemistry of stress vulnerability and the stress response is the essence of most (if not all) stress-related mental and neurologic diseases, with depressive states being prime example. The neurochemistry of depression is, in fact, the neurochemistry of an abnormal stress response. The stress response may have to be measured; important goals of translational studies include validation of animal models of depression and unification of physiological and biochemical indices of the stress response for comparative analysis of different models and data from depressive patients, as well as elaboration of valid indices of the stress response for patients. For these purposes, it is critical to non-invasively analyze biomaterials such as saliva and hair.

Keywords: stress, stress response, hypothalamo–pituitary–adrenal axis, cortisol, corticosterone, neuroendocrine system, depression, brain, neurochemistry

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In addition to "Pressure or tension exerted on a material object" the Oxford dictionary gives the following definition of stress: "A state of mental or emotional strain or tension resulting from adverse or demanding circumstances." The term stress was introduced in the biomedical field by Cannon [1] and further given a major meaning in 1936 by Selye [2], who defined stress as a general reaction of adaptation, a non-specific response to any demand that cannot be abolished since it is part of the existence of an organism. Many of the biological indices of the internal milieu described by Claude Bernard remain stable (homeostasis), while other indices may be changed; these adaptive changes underlie the concept of allostasis developed by McEwen [3, 4].

Stress, as an adaptive response of the body, is controlled by the brain. The main brain areas involved in stress are the prefrontal cortex, the hippocampus, and the amygdala, which represent the limbic system, and the hypothalamus. The stress response may be represented as a set of measurable biochemical and physiological events, whose validation is an important goal of translational studies. The main systems of the early stress response include the autonomic nervous system (primarily, sympathetic), the neuro-endocrine system, and the immune system.

The neuroendocrine system is a key player in the stress response (Fig. 1). The major neuroendocrine cascade, the hypothalamo–pituitary–adrenal axis (HPAA), involves the hypothalamus, which secretes corticotrophin-releasing-hormone (CRH) as a response to the information received from the (prefrontal) cortex and the limbic system. CRH and other factors secreted by the hypothalamus stimulate the anterior pituitary, which in its turn releases corticotropin (adrenocorticotropic hormone, ACTH); this induces the synthesis and secretion of cortisol (corticosterone in animals) from the cortical part of the adrenals. The release of a number of other hormones is also induced by hypothalamic factors resulting in secretion from the anterior pituitary of factors that stimulate release of peripheral hormones. The "built-in safety systems" of the brain [5], which form feedback loops, make it possible that the excess of cortisol in the blood signals the brain (via the hypothalamus and pituitary) and adrenals to reduce cortisol production. However,

[1] Corresponding author; address: ul. Butlerova 5a, Moscow, 117485 Russia; phone: +7(495)952-4007; e-mail: nata_gul@pisem.net.

Abbrevations: ACTH, adrenocorticotropic hormone; CORT, cortisol (corticosterone); CRH, corticotropin-releasing hormone; HPAA, hypothalamo–pituitary–adrenal axis; LS, limbic system; PFC, prefrontal cortex.

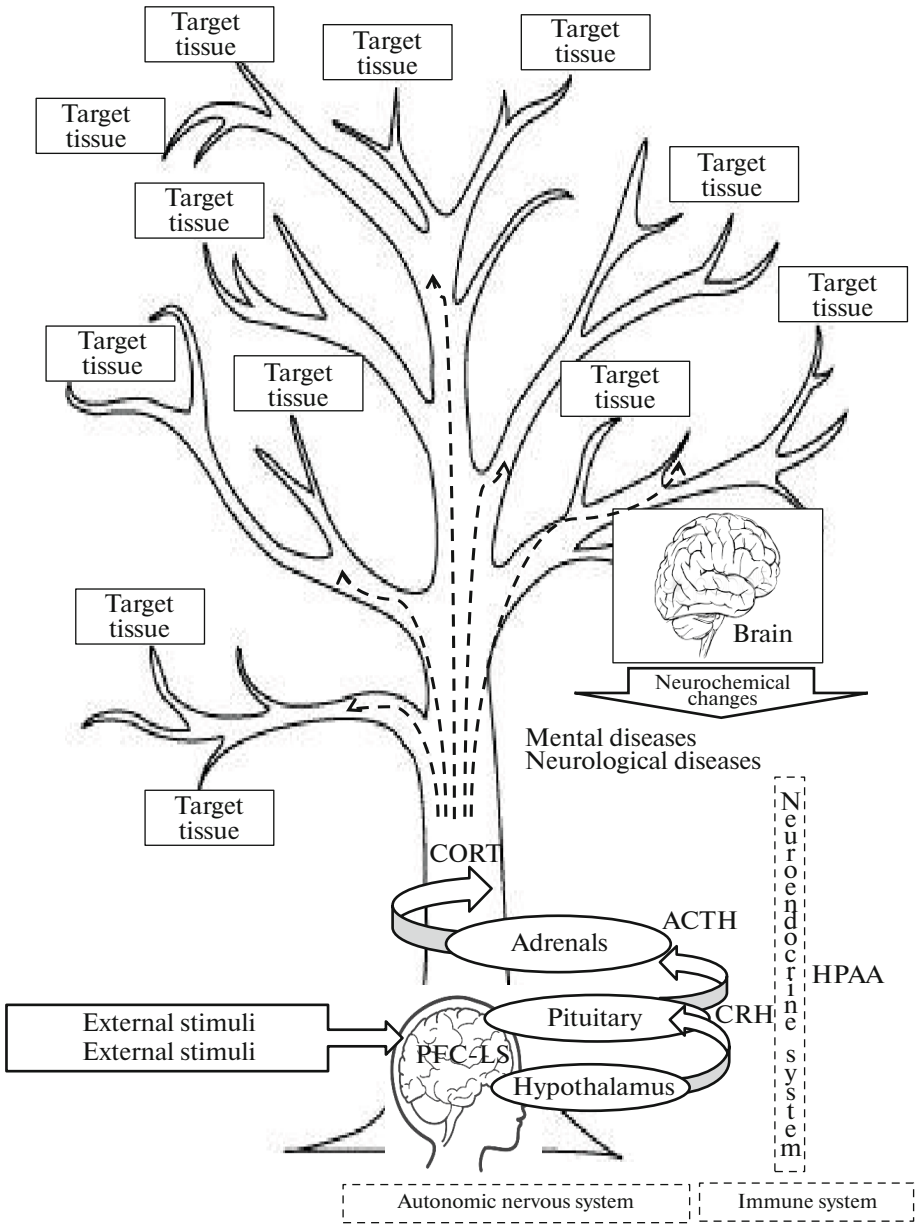

Fig. 1. The tree of the HPAA-mediated stress response. Biphasic key neurochemical HPAA-related changes in the brain induced by stress factors. The initial phase of the stress response takes place in the brain and includes the release of CRH from the hypothalamus inducing secretion of ACTH from the pituitary. Cortisol (corticosterone) released from the adrenals into the blood reaches all organs and tissues that express corticosteroid receptors in cells and, thus, are targets for this hormone. The brain itself is among these organs; thus, stress-induced events in the brain that stimulate cortisol secretion are followed by cortisol entering the brain and beginning corticosteroid signaling, which is the second brain-associated phase of the stress response.

under continuous stress, this feedback system stops functioning, and the hypothalamus continues CRH production and stimulation of ACTH release from the pituitary, thus, stimulating cortisol secretion [6]. Excessive cortisol signaling through mineralocorticoid and glucocorticoid receptors is harmful for the hippocampus [7]. It was noted long ago that the excess of cortisol related to an acute severe or chronic stress can damage hippocampal neurons, decrease neurogenesis, and give rise to cognitive troubles. A number of recent studies confirmed the association between stress and neurodegenerative and mental diseases; a cortisol excess plays a major role in this association [8–10]. The stress response involves the modulation of the immune system and the pro-inflammatory effects of stress are believed to favor the occurrence of

chronic diseases [11–13]. Stress-induced overproduction of pro-inflammatory cytokines is closely related to the excess of cortisol/corticosterone [14]. HPAA dysfunction impairs neuroplasticity, thus creating paths for a large variety of neuropathologies [15–17].

In a sense, regarding the stress-induced main neuro-endocrine cascade, the basic neurochemistry of the stress response is like a tree (Fig. 1). The brain plays a dual role as a primary sensory organ that perceives stress factors and induces a flow of hormonal "tree saps" and as a secondary sensory organ that embraces signals that are transmitted via these hormones. Many smaller branches signaling to different organs and transduction pathways in these organs and tissues grow out from the main endocrine stem and major branches of HPAA. These branches are associated with all of the tissues of the body, since stress hormones cortisol/corticosterone and epinephrine have receptors in virtually all types of cells. In fact, higher (cerebral) levels of HPAA represent the primary starting point of stress neurochemistry (Fig. 1).

The brain itself is the most important organ in orchestrating the neuroendocrine, autonomic, and immune responses. At the early phase of the stress response, HPAA and sympathetic/epinephrine influences are involved as is well known; however, we can hardly predict the final events. However, many signaling pathways stimulated by HPAA have been discovered and many possibilities exist for switching between these signal transduction pathways and for combining them; numerous factors would determine the involvement of definite mechanisms in the stress response. Stress sensitivity and the stress response are individual characteristics. In fact, every individual reacts differently to stress depending on its specific features (mental and physical status, age, gender, constitution, life experiences (both early and adult), genetic background, etc.) [5, 18, 19]. Epigenetic alterations, including those in early life, contribute to genomic programming and, thus, to the individual stress response and stress sensitivity [20, 21].

An aberrant neurochemistry of stress vulnerability and the stress response is the essence of most (if not all) stress-related mental and neurologic diseases, with depressive states being prime example [22–25]. The neurochemistry of depression is, in fact, the neurochemistry of an aberrant stress response. Since the stress response can be measured, important goals of translational studies are a) validation of animal models of depression [26]; b) unification of physiological (behavioral) and biochemical indices of the stress response to enable comparative analysis of different models and data from depressive patients [27, 28]; and c) elaboration of valid indices of the stress response for patients. The latter goal demands specific efforts, since reliable non-invasive methods should be developed that adequately reflect the mechanisms of the stress response. For this purpose, analyses of biomaterial, such as saliva and hair, are critical [29, 30].

COMPLIANCE WITH ETHICAL STANDARDS

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