REVIEWS

Devoted to the 60th anniversary of H. Selye's bold delving into mysteries of nature, which stimulated many inquisitive minds to engage in exploring stress

New Accents on the Classical Concept of Stress

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The evolution of H. Selye's classical concept of stress is discussed. It is shown how the general notions of stress have transformed into a concept of emotional stress as the primary emotional response of humans and animals to stressors. The leading role of conflict situations in the genesis of emotional stresses is validated in terms of P. K. Anokhin's general theory of functional systems. In contrast to H. Selye's view that the general adaptation syndrome caused by stress is nonspecific, specific manifestations of stress in the activity of various functional systems are postulated. New concepts are formulated concerning an individual approach to the investigation of various stress indicators, changes in brain functions occurring during stress (including activation of the early genes and lipid peroxidation) that give rise to psychosomatic disorders, the contribution of limbic-reticular structures to the generation of "stagnant" emotional excitation which underlies psychopathology, and the role of oligopeptides in the mechanisms of resistance to emotional stress.

Key Words: *stress; emotional stress; conflict situations; functional systems; limbic and reticular structures; early genes; lipid peroxidation; oligopeptides*

The concept of stress proposed by H. Selye [52] has gained wide acceptance both in experimental research and in clinical practice. H. Selye, who borrowed the term "stress" from physics, defined stress as a load on the organism resulting from its exposure to adverse stimuli (stressors). According to Selye, stress is based on a nonspecific adaptation syndrome characterized by activation of the hypothalamus—anterior pituitary—adrenal cortex system. The classical manifestations of stress, such as adrenal hypertrophy, involution of the thymus and lymph nodes, and ulcerative lesions of gastric mucosa, develop under the influence of pituitary hormones [53]. In recent years, general theoretical notions of stress have been considerably expanded. It has been shown that stress affects the function of thyroid gland [37], reproductive system [1], heart [21], and brain [11,38] and modifies circulation [36], oxygen-supplying mechanisms [18], blood parameters [7,8], immunity [50], and catecholamine levels in the blood, urine, and various brain structures [5,12,13,55].

Thus, stress manifests itself as a complex **systemic response of the organism**. This generally recognized concept of stress is based on the principles of the reflex theory: stressful stimulus → reflected response of the organism.

On the other hand, L. Levi *et al.* have formulated a concept of emotional stress (ES) [42,45] which is based on the W. Cannon concept [41] on

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the role of the sympathetic nervous system in the development of emotional reactions and on the P. MacLean's theory [47] concerning the contribution of emotions to the genesis of adaptive responses in animals and humans. According to L. Levi, ES reflects the emotional response of a human being to stressors. Thus, H. Selye's concept of stress began to be actively transformed into **the concept of emotional stress**.

This concept of emotional stress is consistent with the views of the Russian scientists developing I. M. Sechenov's and I. P. Pavlov's theory of nervism [2,7,17,22,23] which regards negative emotions induced by stress as an important factor in the development of various pathologies.

Stress as an emotional response of the organism

Human beings primarily respond to their internal states and to the environment (objects, animals, and especially people) by negative (grudge, resentment, fear, anger, anguish, aversion, envy, hate, etc.) and positive (joy, pleasure, happiness, delight, satisfaction, etc.) emotions. Emotions serve as "direction finders" enabling individuals to express their attitude to the surrounding objects and to other individuals [3].

Emotions usually precede overt acts or actions. Of particular significance is the "direction-finding" role of negative emotions which become more intense whenever the individual feels a vital need for, but is incapable of, achieving socially or biologically significant results. In such cases negative emotions are a source of internal energy that mobilizes the organism. They actively motivate the individual to overcome obstacles, often with increased inventiveness.

Under normal circumstances, negative emotions are usually short-lived, episodic, and, once the desired goal has been achieved, transform into positive emotions which serve as a kind of reward for the efforts made in attaining the goal and/or in meeting the perceived needs. But if an individual is for a long time beset by difficulties in trying to achieve the required results, negative emotions sum up to acquire the form of strongly marked and constant irritation, anger, indignation, and affects or, on the contrary, of insuppressible anguish and depression, and in such cases they transform into emotional stress.

Theory of functional systems and concept of stress

In contrast to the reflex theory, the theory of functional systems proposed by P. K. Anokhin [4] postulates that the results of actions rather than reflected actions are the leading factors organizing the response to stressors. From this viewpoint the organism is regarded as the sum of many functional systems integrated on the principles of hierarchy, multiply connected regulation, and sequential interaction with each system determining the optimal state of a particular adaptive result useful for the organism. The significance of each adaptive result is determined by metabolic manifestations and depends on the activities of other functional systems [31].

According to the theory of functional systems, ES evolves in so-called conflict situations, where an individual motivated by biological or social need for a long time faces a limited or no possibility of satisfying that need. In such cases, i.e., when it is difficult or impossible to achieve the appropriate adaptive result, the intensify of negative emotions increases considerably, and after summation they tend to generate a state of "stagnant" stationary excitation of the brain. Owing to generalized propagation through the somatic and autonomic nerves and hormonal hypothalamic-pituitary mechanisms, negative emotions influence virtually all tissues in the body to induce systemic stress reactions.

Individual reactions to conflict situations

H. Selye and his followers have employed averaged physiological and biochemical parameters in the analysis of various manifestations of stress. However, we have noticed that the response to the same stressor varies from animal to animal [25,32,33].

For example, after a 30-h immobilization in a very small box, some rats exhibited no changes in arterial pressure (AP) and heart rate, others developed transient hypo- or hypertension, and many rats died (gradual decline in AP was observed in some of them and hypertensive crisis in others, with a sharp rise and fall of AP [26]). Autopsy revealed thymic involution and adrenal hypertrophy in rats of all three groups, which was regarded as an indicator of stress. A similar individual variability of cardiovascular reactions was documented in immobilization and cutaneous electric stimulation experiments on rabbits [34]. The proportions of rats resistant, adapting, and prone to stress-induced cardiovascular disorders are different in different strains [39]: the resistance of Wistar and WAG rats to stress proved to be higher than that of August rats.

However, the level of adrenergic innervation of the stomach in Wistar rats, whose cardiovascular system was resistant to ES, was increased; the rats developed multiple erosions and ulcers of the mucous membrane of the pyloric part of the stomach [15]. In the water-immersion stress model, the occurrence

of ulcerative lesions in Wistar rats was higher than that in other strains [24,49].

The pituitary-thyroid system participates in the development of the stress reaction from its very beginning [37]. Activation of sex hormones was observed in female rats subjected to ES [1].

Thus, ES manifests itself as changes in various functional systems and triggers nonspecific hypothalamic-adrenal reactions. In similar conflict situations ES induces cardiovascular, gastrointestinal, endocrine, and other disorders. Individual resistance to changes in some physiological functions may coincide with susceptibility to changes in other functions. Different functional systems show different resistance to stressors in conflict situations. Proceeding from general theory of functional systems, ES can be regarded as a factor selectively impairing autoregulation of less resistant functional systems [27,28]. Consequently, ES involves both nonspecific and specific systemic hormonal and tissue mechanisms.

Individual resistance and susceptibility to ES has been observed in humans [43,51].

Individual approach to the analysis of various manifestations of ES has been applied in some investigations [6,9,10,19,20]. However, the overwhelming majority of publications [14,27] dealing with various aspects of stress still contains averaged heterogeneous experimental data that are unlikely to reflect the true nature of ES.

The discovery of individual resistance of physiological functions to stressors in various conflict situations opens new prospects both for prognostic evaluation of individual resistance and for correction of weakened functions in stress-prone individuals.

The primary response of limbic-reticular structures to ES

In contrast to Selye's theory that interprets activation of the hypopthalamic—pituitary—adrenal cortex axis as a universal response to stressors, the concept of ES considers emotions as a primary reaction in a conflict situation. It was demonstrated that limbic-reticular structures of the brain are the morphofunctional substrate of emotions [47].

In our studies, ES-generating subthreshold electrical stimulation of the defensive centers in the ventromedial hypothalamus of immobilized rabbits elicited primary changes in electrical activity (desynchronization of the EEG and ordered rhythm of 4-6 waves/sec) only in limbic-reticular structures. At higher intensity of stimulation the same changes occurred in the cerebral cortex; further increase in the stimulation intensity induced changes in heart and respiration rates and in AP. Evoked potentials were also first recorded from limbic-reticular structures and only later from the cerebral cortex [56].

Hormonal and vascular reactions and other autonomic components of ES were not observed in animals with destroyed septal area and reticular nuclei of the mesencephalic tectum. However, these reactions were enhanced in animals with bilaterally destroyed basolateral part of the amygdala. There was no elevation of blood pressure associated with hydrocortisone and epinephrine in stressed animals with destroyed reticular nuclei in the mesencephalic tectum. Similar results were obtained in experiments with the α-adrenergic blocker aminazine (chlorpromazine), indicating that the reticular formation is a secondary site for adrenal hormones in ES. Vascular hypertensive reactions to electrical stimulation of the ventromedial hypothalamus were restored in adrenectomized rabbits given microinjections of hydrocortisone and epinephrine [26].

Thus, our findings indicate that vascular hypertensive and other vegetative reactions observed in ES develop through primary excitation of limbic and reticular structures and their effects on brain structures. Emotional excitation arising in a conflict situation first spreads over these structures, and integrated excitation then expands to the effector autonomic centers.

From these findings we have concluded that hypothalamic, limbic, and reticular structures, in which excitations circulate for a long time in special closed circuits [47], can be regarded as the morphofunctional basis for the "stagnant" emotional excitation that impairs the mechanisms genetically weakest among those responsible for autoregulation of functional systems in the body.

In emotional stress, the early gene *c-fos* is selectively expressed in the hypothalamic paraventricular nuclei, limbic system, brain stem, and prefrontal and orbital cortex [44,48,58].

Limbic structures, including hypothalamus, are the sites where ES induces primary changes in lipid peroxidation and formation of free radicals [46,54].

From these data it can be concluded that the primary response to ES involves changes in limbic-reticular structures of the brain and that Selye's adaptation syndrome reflects secondary somatoautonomic reactions to conflict situations.

Changes in the chemical properties of limbic-reticular structures during the genesis of "stagnant" negative emotions

We have found that in animals exposed to ES-generating conflict situations a microiontophoretic application of the neurotransmitters norepinephrine (NE), acetylcholine, and serotonin induces considerable changes in chemical properties of the limbic-reticular

complex and cerebral cortex. Most pronounced changes were observed in the sensitivity to NE [29].

Thus, ES alters chemical properties of the brain and establishes a new neurochemical integration, primarily in the limbic-reticular structures.

Different neurotransmitter mechanisms operate in the brain of rats with different susceptibility to ES.

In Wistar rats (their cardiovascular system is more resistant to ES than that of August rats), the NE content is significantly higher in the hypothalamus, while the dopamine content is lower in the isthmus and mesencephalon.

In immobilization stress, hypothalamic NE levels decrease both in Wistar and August rats, the decrease being more pronounced in ES-resistant rats than in ES-prone rats.

Adaptation to chronic ES led to normalization of lowered NE concentration in the hypothalamus with a simultaneous increase in the mesencephalic NE content and the hypothalamic dopamine content. A single conflict-generating immobilization of adapted rats caused no decrease in hypothalamic NE content, implying reorganizations of the catecholamine metabolism in the hypothalamus of adapted rats, which may account for the resistance of these rats to ES.

These findings indicate that ES modulates the neurotransmitter levels in hypothalamic and reticular structures. We believe that these modulations underlie plastic rearrangements of emotional excitation generated in response to long-lasting conflict situations and the transformation of this excitation into a stable, stationary form [30].

Our studies have shown that ES alters the sensitivity of cerebral cortical and subcortical neurons to microiontophoretically applied oligopeptides [29, 40], and that substance P (SP) significantly increases the sensitivity of neurons in the ventromedial hypothalamus to microiontophoretic application of NE [40].

Alterations in the sensitivity of brain neurons to biologically active substances are of a complex integrative nature, with some neurons becoming more sensitive to neuropeptides and neurotransmitters and other neurons less sensitive. The brain as an integrated whole alters its neurochemical properties in conflict situations.

The alteration of chemical properties by brain neurons underlies, as we believe, the formation of "stagnant" excitation in ES [29].

Oligopeptides in the mechanisms of resistance to ES

Our investigations have shown that the resistance of animals to ES is determined by the brain levels of oligopeptides.

We have demonstrated that hypothalamic levels of SP, delta sleep inducing peptide (DSIP), and β-endorphin are higher in ES-resistant Wistar rats [57].

A single intraperitoneal injection of SP significantly prolonged the survival of ES-prone rats exposed to chronic ES and mitigated the classical manifestations of stress such as adrenal hypertrophy, thymic involution, and ulceration of the stomach mucosa. Administration of SP led to a transient increase in the NE and dopamine contents in hypothalamus and mesencephalon; the effect coincided with the SP-induced increase in the resistance to ES. It should be noted that the hypothalamic NE content was increased to normal values, while the dopamine content in the hypothalamus and mesencephalon increased significantly.

Administration of DSIP increased the resistance of rats to acute ES, judging from a significant rise in the survival values. DSIP also modified catecholamine levels in the hypothalamus and hypothalamoreticular structures [29]. Moreover, it markedly increased the hypothalamic SP concentration and caused opposite changes in hypothalamic and blood levels of β-endorphin and corticosterone [57]. The SP—DSIP combination normalized the cardiovascular functions in ES [35,39].

Special experiments showed that DSIP restores to the original level the ES resistance in rats with destroyed mesencephalic tectum and reticular formation [30].

Investigations of changes occurring in brain neurochemical mechanisms in ES led us to a fundamentally new conclusion: the original chemical integration of molecular structures in the brain is disrupted in ES-generating conflict situations with the formation of another (modified) organization of these structures, leading to the development of a "stagnant" emotional excitation which underlies psychosomatic disorders.

The ES-induced alterations in brain at the molecular level are "fixed" by specific oligopeptides and may persist for months and years. This state can be alleviated or normalized by SP, DSIP, β-endorphin, prolactin, and some others. Oligopeptides synthesized in the brain perform various functions in relation to ES. Some of them determine the initial resistance to ES by restricting the development of neurochemical changes in the hypothalamic—limbic—reticular complex, thus preventing the development of "stagnant" emotional excitations. Others facilitate the summation of emotional excitations and "fix" molecular disintegration, providing the establishing of "stagnant" emotional excitations and determining predisposition to ES. For example, summation and fixation of central excitations are facilitated in animals with low levels of SP, DSIP, and some other oligopeptides in limbic and reticular structures. Intracerebral administration of

these oligopeptides can alter genetically determined or acquired neurochemical integration of brain structures and thus increase or decrease the resistance to ES. Finally, some oligopeptides eliminate pathological disintegration at the molecular level and normalize the state of the brain [29,40].

The nature of "stagnant" emotional excitation at the neurochemical level can be regarded as polychemical. In addition to oligopeptides, it involves neurotransmitters, which act via neurons, and glial elements of the brain.

Our data indicate that oligopeptides play an important role in the cerebral mechanisms of resistance to ES.

Central mechanisms responsible for the resistance to ES are based on the specific integration of molecular and neurochemical properties of neurons in the emotiogenic hypothalamic—limbic—reticular structures [29]. Impairment of this integration results in the formation of a stable pathological determinant [16] leading (on the basis of continuous descending influences) to disturbances in the mechanisms responsible for autoregulation of the major functional systems and to the development of psychosomatic diseases.

Thus, brain functions are the primary factor determining psychosomatic disorders in ES.

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