

HYPOTHALAMO-PITUITARY-ADRENOCORTICAL AND SYMPATHO-ADRENOMEDULLAR SYSTEMS IN STRESS RESPONSE

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Summary: The hypothalamic-pituitary-adrenocortical and sympatho-adrenomedullar systems are major effector systems that serve to maintain homeostasis during exposure to various stressors. The neurochemical pathways controlling activation of hypothalamic-pituitary-adrenocortical and sympatho-adrenomedullar systems are of special interest. Catecholamines, present in specific brain areas as well as in peripheral tissues are responsible for adequate stress response regulating the relationships between the hypothalamic-pituitary-adrenocortical and sympatho-adrenomedullar functions. In last decade, numerous studies have demonstrated differential sympathoneural and adrenomedullary responses during exposure to different stressors. Some stressors provoke the strongest reaction of adrenocortical activity than that of adrenomedullary, while others do the opposite. Each type of stressor has its own central neurochemical and peripheral neuroendocrine »signature« with quantitative and qualitative distinct mechanisms.

Key words: stress, ACTH, glucocorticoids, catecholamines

»Health consists of a harmonious balance with the surrounding world, while disease arises from challenges to that balance«

Hippocrates (400 b.c.)

Introduction

The constancy of the internal milieu or homeostasis is critical for survival and independent existence of higher organisms. The preservation of internal environment requires continuous adaptation to external or internal stimuli, involving behavioral, visceral and endocrine changes necessary for controlling the disturbance (1). The world is not perfect and living organisms are constantly challenged by this imperfection. Facing various numerous environmental changes organisms have evolved an entire physiological system to buffer themselves from these perturbations and to reestablish balance (2). If external or internal stimuli are too strong or persist for a long time they can be considered as a stressor which causes various stress-responses in the body and provoke the state of stress.

It is an obligation of all stress physiologists to point out some confusion of terms stressors, stress-response, stress. A stressor is anything that disrupts physiological balance and stressor-response is the body's adaptation designed to reestablish the balance. Stress can mean the cause that creates an imbalance, the response of organism to it, or both it can informally refer to the general state of stressors provoking stress-response (3–5).

Two endocrine systems dominate in stress - both involve the adrenals: cortex that secretes glucocorticoids and medulla that secretes adrenaline, the most famous hormone of stress response. Hans Selye was the first to discover the role of glucocorticoids and Walter Cannon the role of adrenaline in stress. They both emphasized the nonspecificity of stress response very different situations trigger the same response. Cannon termed the burst of adrenaline in stress as *flight or fight response* and Selye, the glucocorticoid secretion as *general adaptation syndrome* (2).

What is the purpose of hormonal changes in stress? Why the variety of stressors elicits a relatively consistent set of responses? Is being hungry and predatory (lion hunting zebra) or frightened and injured (zebra escaping from lion) similar or different physiological state concerning the reaction of endocrine systems, hypothalamic-pituitary-adrenocortical (HPA) and sympatho-adrenomedullar (SA) in stress? Orga-

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nisms in the state of stress have an immediate need for energy. The metabolic hallmark of the stress-response is the need to mobilize energy for immediate use. Energy storage is inhibited and preexisting stores of energy are broken down into simpler, more easily utilized form in the blood stream, glucose (1).

Increased glucocorticoid level in stress, in addition to its role in maintaining energy supply, modulates cognition, immune and cardiovascular responses (6). They also contribute to the visceral responses to stress by stimulating catecholamine synthesis and modulating their metabolic and cardiovascular effects (7-9). It should be pointed out that the additional important role of glucocorticoids in stress is to prevent threats to homeostasis from exaggerated reactions (10). Thus, some authors claim that the physiological function of stress-induced increases in glucocorticoid levels is to protect not against the source of stress itself, but against the normal defense reaction that are activated by stress (11).

Endocrine systems stimulated by stressors

Hypothalamic-pituitary-adrenocortical system

The major endocrine mechanism in stress is the activation of hypothalamic-pituitary-adrenal axis, resulting in rapid secretion of circulating corticotrophin (ACTH) and subsequent rise in glucocorticoids (12, 10). Three basic patterns of HPA response, depending on the type of stress are identified: a) desensitization of ACTH responses to the sustained stimulus, but hyperresponsiveness to a novel stress despite elevated plasma glucocorticoid levels, as occurs in physical-psychological stress; b) no desensitization of ACTH response to the repeated stimulus and hyperresponsiveness to a novel stress, as occurs during repeated painful stress and insulin-induced hypoglycemia; and c) small and transient increase in ACTH, but sustained elevation of plasma corticosterone and diminished ACTH responses (1).

A stressor is perceived and processed by different regions of the brain which transmit the signals further to the hypothalamus, causing the release of corticotrophin releasing hormone (CRH) and related secretagogues (vasopressin, prolactin, β -endorphin etc.) which enter the hypothalamic-pituitary portal circulation and triggers anterior pituitary ACTH release. During stress the increase in CRH secretion occurs within a few seconds, ACTH within 15 seconds and glucocorticoids within a few minutes. However, the picture of HPA reaction to stressors is far more complicated than this, as CRH is only one of a potentially half a dozen hypothalamic hormones that regulate ACTH release from the pituitary (13). The CRH synthesizing and secreting neurons, which influence ACTH secretion, are located in the paraventricular nuclei (PVN) projecting to the outer part of median

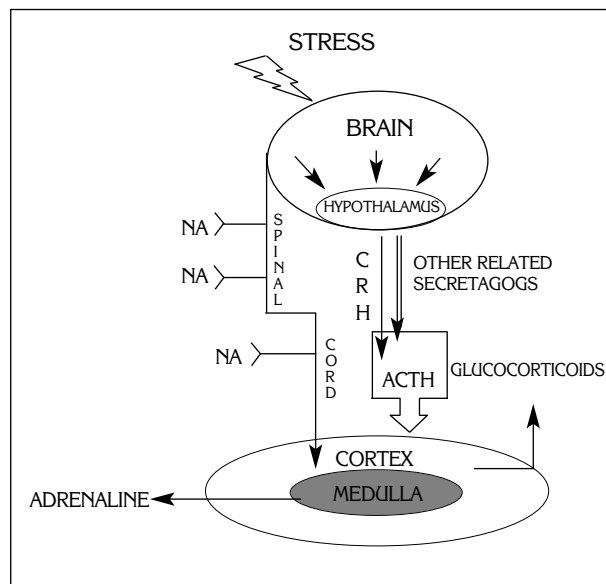


Figure 1. Stress-induced activation of hypothalamic-pituitary-adrenocortical and sympatho-adreno medullary systems

eminence (11). Vasopressin and oxytocin are synthesized in the magnocellular neurons, having nerve terminals in the posterior pituitary (14). Under basal condition vasopressin concentration in the hypothalamic-pituitary portal system is in traces whereas in stress conditions, such as adrenalectomy, repeated immobilization, insulin-induced hypoglycemia, chronic psychosocial stress it is rapidly increased (1). It seems, however, that vasopressin itself is a weak stimulator of ACTH secretion but it strongly potentiates CRH effect by increasing IP_3 concentration and calcium channel opening on corticotrophin cells in the anterior pituitary (15, 16). CRH induces an increase in cAMP concentration and calcium channel opening by activating G-proteins and adenylate cyclase, which together with vasopressin effect, elevates ACTH release (17). In addition, CRH induces an increase in proopiomelanocortin (POMC) gene expression and consequently stimulation of ACTH synthesis (1).

Despite abundance of published data, central mechanisms that trigger the HPA activity producing elevated ACTH and glucocorticoid secretion in stress, are still obscure. There are neuronal pathways to CRH-secreting neurons that originate in the brain stem and involve catecholaminergic axons (18) as well as non-catecholaminergic ones that secrete various neurotransmitters such as neurotensin, neuropeptide Y, bombesin, inhibin beta, enkephalin, somatostatin (19). Numerous serotonergic axons, originating from the mesencephalon, also regulate CRH release (20). Brain catecholamines, as neurotransmitters, play a considerable role in the activation of HPA axis both in basal and stress conditions. Adrenalectomy induces an increase in hypothalamic noradrenaline (NA) content accompanied by a decrement of circulating glu-

Table I Different activation of ACTH and corticosterone release in response to various stressors in rats

HPA SYSTEM	Fasting 48 h	Crowding 3 h	Cold (6 °C) 3 h	Heat (38 °C)	
				20 min	60 min
Blood ACTH concentration	2.4	4.0	2.4	9.0	15.0
Blood corticosterone concentration	1.6	1.6	1.9	1.8	2.6

Numbers in the table represent the multiplication of parameters in comparison to controls.

corticoids (21). Besides, it was shown that glucocorticoids markedly affect catecholamine synthesis, excretion and degradation in various tissues of experimental animals (22-24). The fact that monoamine oxidase (MAO), catecholamine degrading enzyme, is widely distributed in many brain regions (hippocampus, cortex, caudate nucleus, hypothalamus and thalamus) and that the activity of this enzyme is changed in various stress conditions, indicates the intense metabolism of these neurotransmitters in stress (25). The elevation of two forms of hypothalamic MAO activity, A and B was observed in rats treated with ether vapor and sham adrenalectomy (26). Changed daily rhythm of light and darkness, due to keeping the animals under the conditions of continuous light and darkness, induces a significant reduction of hypothalamic MAO-A activity (27). Exposure of animals to extreme environmental temperatures (38 °C for 20 and 60 minutes) provokes a decrement of total MAO activity in rat hypothalamus, brain stem and hippocampus (28, 29). These changes in the brain MAO activity are accompanied by a significant increment of circulating ACTH and corticosterone concentration (28, 30). In contrast, MAO activity in the hypothalamus and hippocampus of animals exposed to a metabolic stressor, a 48 hour fasting, rapidly elevates, followed by intense secretion of both ACTH and corticosterone (28, 31). Bearing in mind that MAO is the enzyme involved in catecholamine degradation, the changes in its activity are an important indicator of changes in its substrate (catecholamines) concentrations and could point to their role in neuronal transmission in stress conditions (32). It was shown that the concentration of catecholamine metabolites in the hypothalamic preoptic area is decreased and concentration of catecholamines themselves is increased in heat stressed sheep (33, 34). Many studies have demonstrated changes in cerebral catecholamine metabolism by stressful treatments inducing, in general, an increased noradrenaline metabolism and less consistent effect on serotonin and dopamine. Cold restraint, mild foot shock stress and conditioned fear all result in an increased level of dopamine metabolites in the prefrontal cortex whereas immobilization stress results in the increased synthesis of this amine in the mesolimbic dopamine neurons (35). Reciprocal reverberatory neural connections occur between CRH and brainstem NA neurons of the central stress system, with CRH and NA stimu-

lating each other. Selfregulatory ultra short negative feed-back loops are also present in both the PVN CRH and brainstem NA neurons, with collateral fibers inhibiting CRH and catecholamine secretion (36).

According to the original stress concept, introduced by Hans Selye and Walter Cannon, stress was defined as non-specific response to stressors always inducing the activation of adrenal glucocorticoid and catecholamine release. However, over the course of the last years a large amount of accumulated data suggests that the reaction to stressors could be specific, depending on the type of stressor, duration of exposure etc. Studies, using a wide variety of stressors, clearly indicate that a pattern of neuroendocrine response is dependent upon the stress stimulus applied (37-39). Substantial stressor specificity has been demonstrated in the activation of HPA axis and sympathoadrenal system, known to be the main stress systems, in both humans and experimental animals (40, 41).

Plasma ACTH concentration elevates quantitatively differently under the influence of various types of stressors applied (crowding, heat, cold, fasting). The most intense ACTH increase is provoked by a 60 and 20 min heat exposure, as well as by crowding stress, being 15, 9 and 4 times as much as that of controls, respectively (30). On the other hand, fasting and cold stress are weaker stressors, as compared to those of heat and crowding, as they produce a 2.4 times increment of ACTH concentration. This is in agreement with other findings (38), indicating that the increment in plasma ACTH is larger under the influence of immobilization stress in respect to cold stress and insulin-induced hypoglycemia. It seems that ACTH secretion, provoked by low plasma glucose level, is driven only 60% by CRH itself and the remaining 40% is driven by CRH-independent mechanisms probably also originating from the hypothalamus (42). During immobilization stress CRH secretion rate is 9 times higher than that observed during hypoglycemia (43).

Pituitary response to acute stress is rapid and so is the return to prestress level, except for corticosterone (CORT) (44). Plasma CORT levels is elevated in response to psychophysical stressor, presumably being significantly greater in response to physical one (45). The greatest increase in CORT synthesis appears under the influence of environmental stressors, heat

and cold, lasting for 60 min and 3 h, respectively, each producing a 2.3 times decrement in the adrenal cholesterol concentration. CORT synthesis is followed by an intense CORT secretion under the influence of a 60 min heat and 3 h cold exposure. Crowding, as psychological stressor, seems to be the weakest stressor concerning the activation of CORT synthesis. This is in agreement with other findings that compared the effects of psychological and physical stressors on peripheral CORT concentration (46).

As discussed, CRH is not the only hypothalamic hormone that triggers ACTH release. Numerous »secretagog« hormones carry out that task. At the hypothalamic level, there appears to be a stressor-specific coding, different stressors cause a different profile of the secretagogos to be released. Probably, these secretagogos have additional and different roles at the pituitary level which modulates the whole response of HPA axis (2).

Sympatho-adrenomedullar system

The sympathetic nervous system, activated in stress, releases noradrenaline (NA) from most of its nerve endings which have projections in almost each body organs. Besides, sympathetic relays originating in the spine terminate in the adrenal medulla and stimulate the release of adrenaline (A) within the seconds.

Catecholaminergic system in the brain and peripheral tissues are among the first to be activated during the stress response. The intensity of its activation is evaluated by the decrement of its concentration in the tissues (47, 48), increment in the circulation (49), intensification of its urinary excretion (47) and its increased release from catecholaminergic neurons in various brain regions (50). The increased catecholamine concentration in the sympathoadrenal and brain catecholaminergic systems, among others, is due to elevated activation of tyrosine-hydroxylase (TH) (51), dopamine-beta-hydroxylase (DBH) (52), phenyletanolamine-N-methyltransferase (PNMT) (53), enzymes that are involved in catecholamine synthesis, or lowered activation of the degrading one, MAO (54).

Two branches of sympathoadrenal system are activated in stress depending on the type of the stressor (55), which induces different responses of the adrenal medulla and peripheral sympathetic nervous system (56). In rats exposed to forced swimming for the first time, dissociation of adrenal and sympathetic function occurs. Initially A secretion from the adrenal medulla was increased as the consequence of unknown experience and incapability to predict the following events – emotional stress. However, when animals are trained to the same stressor the neuronal part of the sympathoadrenal system is activated with increased secretion of NA from its nerve terminals (53). Similar results are obtained when animals are exposed to cold; the adrenal medulla is activated at the beginning and sympathetic nervous system after prolonged exposure (57). The intense increment of A secretion was observed under the effect of immobilization, hemorrhage, pain and insulin-induced hypoglycemia (50). The results with metabolic stressor, both fasting and insulin-induced hypoglycemia, are contradictory. Namely some results show the increased A and decreased NA secretion (58, 59) and others confirm the increase in NA release probably from the adrenal medulla itself given that 30% of blood NA content originates from the adrenals (59). Besides, it is possible that A itself, binding to the presynaptic adrenergic receptors, stimulates NA release (60).

DBH, the enzyme which transforms dopamine to NA changes its activity in response to various stressors and induces the increase in catecholamine synthesis. However, the quantitative differences in its activity are present. The greatest increment in the adrenal DBH activity occurs under the influence of extreme environmental stressors, cold (6 °C) and heat (38 °C), being about five times greater than in controls (28). Cold stress induces the increased expression of rRNA for PNMT in adrenals as well (61). Crowding, the inability of free moving, caused by placing numerous animals in the single cage (12/cage vs. 2/cage) elevates adrenal DBH activity and A urine secretion but to a lesser extent compared to cold and heat exposure (28). The adrenal reaction is similar after animal's exposure to immobilization stress which is also defined as physical and psychological compound stress (62).

Table II Effect of various stressors on the adrenal DBH activity and urine catecholamine concentration in rats

SYMPATHO-ADRENOMEDULLAR SYSTEM	Fasting 48 h	Crowding 3 h	Cold (6 ³ °C) 3 h	Heat (38 °C)	
				20 min	60 min
The adrenal DBH activity	2.4	1.7	4.5	1.8	3.5
The urine adrenaline concentration	3.6	2.8	2.3		
The urine noradrenaline concentration	3.5	1.7	4.0		

Numbers in the table represent the multiplication of parameters in comparison to controls.

Insulin-induced hypoglycemia provokes an increase in the adrenal TH activity and both mRNA for TH and mRNA for PNMT expression (63), whereas fasting induced hypoglycemia (48 h) causes an increase in adrenal DBH activity accompanied by the increased urine A concentration (28). Higher intensity of urinary A secretion was observed after fasting as compared to its secretion provoked by immobilization, hemorrhage and pain (57, 37, 38). As far as urinary NA secretion is concerned it was shown that animals response was most intense to cold stress, less intense to immobilization and crowding but the least to hypoglycemia (38, 28). It is interesting that some results confirm the increased urinary NA secretion after fasting (28), which is contradictory to the statement that complete food restriction provokes dissociation of sympathetic nervous system and adrenomedullary functions expressed as a decrement of NA and increment of A urinary secretion (57, 64). However, it was shown that insulin-

induced hypoglycemia stimulates, in addition to A, NA secretion from adrenal glands (65).

For Selye, one of the cornerstones of the stress response was its nonspecificity. This was the idea that whether we are too cold or too hot, the stress-response is essentially similar. In the last decade this has turned out not to be the case, not all stressors provoke the identical package of responses. Some stressors provoke the strongest reaction of adrenocortical activity than that of adrenomedullary while others do the opposite. Each type of stressor has its own central neurochemical and peripheral neuroendocrine »signature« with quantitative and qualitative distinct mechanisms (35).

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HIPOTALAMO-HIPOFIZNO-ADRENOKORTIKALNI I SIMPATO-ADRENOMEDULARNI SISTEMI U ODGOVORU NA STRES

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Kratak sadržaj: Hipotalamo-hipofizno-adrenokortikalni (HHA) i simpatoadrenomedularni (SA) sistemi su glavni efektori koji regulišu održavanje homeostaze u toku izlaganja različitim stresorima. Neurohemijski putevi koji kontrolišu aktivaciju HHA i SA sistema su od posebnog značaja. Kateholamini, prisutni u specifičnim regionima mozga, kao i perifernim tkivima su odgovorni za adekvatnu reakciju organizma u stresu, s obzirom da regulišu interakciju HHA i SA sistema. Poslednjih deset godina brojne studije su pokazale da se simpatoadrenomedularni sistemi razlikuju u odgovoru na različite stresore. Neki stresori intenzivnije aktiviraju adrenokortikalni u odnosu na adrenomedularni sistem dok drugi imaju suprotan efekat. Svaki stresor ima sopstveni neurohemijski potpis sa kvantitativno i kvalitativno različitim centralnim i perifernim putevima i mehanizmima delovanja.

Cljučne reči: stres, ACTH, glukokortikoidi, kateholamini

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