Neuroendocrinology of stress and depression

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Summary. The concept and the related definitions of stress were given by Walter Cannon 1914 and Hans Selye 1936. Neuroendocrine answer to stress normally is a mechanism to adapt the organism to different internal or external conditions. The main components of the stress system are the corticotropin-releasing hormone (CRH) and locus coeruleus-norepinephrine/autonomic systems and their effectors, the pituitary-adrenal axis, and the limbs of the autonomic system. The effects of CRH are transferred by two specific receptors linked with protein G: CRH-R1 and CRH-R2. The main negative feedback regulation of hypothalamic neuronal activity is performed by peripheral steroids. Different peptides as argenine-vasopressin activate the HPA system. In human beings atrial natriuretic peptide (ANP) is the only neuromodulator with antianxiety effects that inhibits HPA activity at multiple levels. Evidence for interactions between the nervous and immune systems is discussed. Disturbances in the HPA-axis have an influence of affective state and cognition. CRH appears to play an important role in regulating key neural systems involved in controlling mood, anxiety, feeding behavior, and the interactions between stress and drug addiction. The recent development of selective, small molecule CRH R1 receptor antagonists, which block the effects of CRH both in vitro and in vivo, suggest that these compounds may be effective in the treatment of affective and anxiety disorders.

Keywords: stress, depression, hypothalamic pituitary adrenocortical system (HPA), corticotropin-releasing hormone (CRH), atrial natriuretic peptide (ANP)

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INTRODUCTION

The stress concept is one of the most commonly applied constructs in mental health. The concept and the related definitions of stress were given by Walter Cannon 1914 and Hans Selye 1936 [7, 39, 43]. They discovered that diverse stimuli (stressors) such as hunger, thirst, climatic changes, pain, and different noxious agents cause physiological changes in the animal such as release of adrenal hormones. The term stress today is used in much broader sense [3, 47]. It implicates physical and psychic stressors. Neuroendocrine answer to stress normally is a mechanism to adapt the organism to different internal or external conditions. Emotional or physical stress induces a cascade of changes which leads to a fine tuned answer of the organism. Activation of sympathicus results in higher attention focussed to the trigger and less reproductive activity. Whether the stressing condition is harmless or harmful depends on the way an organism is coping with the threatening situation and whether it regains to homeostasis. A very important part of coping strategy is to finish the answer of the organism when the stressor has passed. If the organism is not able to finish stress-reaction, pathological alterations may result. This condition may be caused by chronic stress exposition. With this implications stress may be measured by monitoring terms of behavioural and physiological alterations that might be indicative for the individual's state of well-being.

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THE STRESS-SYSTEM

The stress system (figure 1) coordinates the generalized stress response, which takes place when a stressor of any kind exceeds an individual threshold. The main components of the stress system are the corticotropin-releasing hormone and locus coeruleus-norepinephrine/autonomic systems and their effectors, the pituitary-adrenal axis, and the limbs of the autonomic system. The stress system is summarized by most of the authors as the hypothalamic pituitary adrenocortical (HPA) stress system. Activation of the stress system normally leads to behavioural and peripheral changes that improve the ability of the organism to adjust homeostasis and increase its chances for survival [8, 44].

Corticotropin-releasing hormone (CRH) is the brain neuropeptide which coordinates the endocrine, autonomic and behavioural responses to stress. CRH producing neurons are localized mainly in the paraventricular nucleus of the hypothalamus. Serotonin (5-hydroxytryptamine, 5-HT)-containing neurons in the midbrain directly

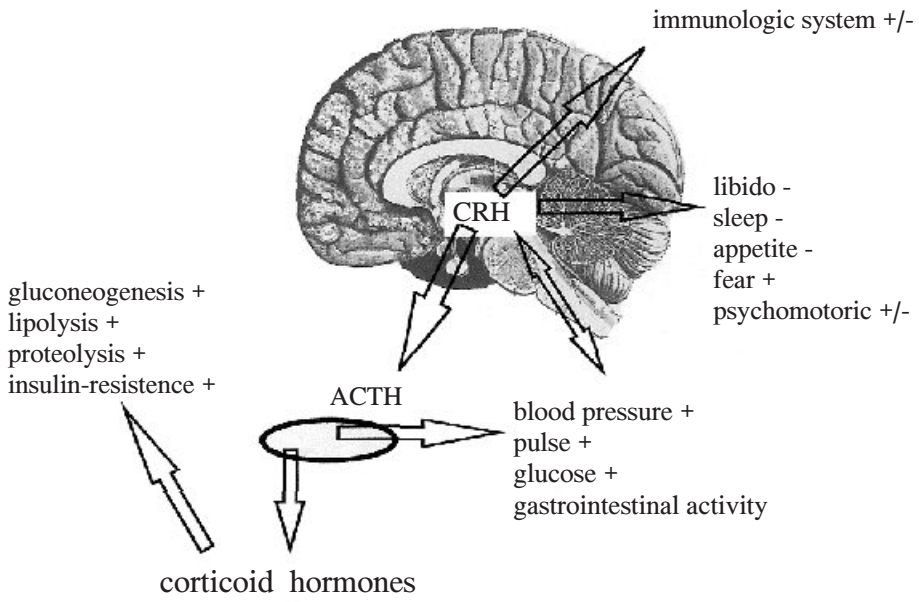

Figure 1. **The stress-system**

innervate corticotropin-releasing hormone (CRH)-containing cells located in paraventricular nucleus of the hypothalamus. Serotonergic inputs into the paraventricular nucleus mediate the release of CRH, leading to the release of adrenocorticotropin, which triggers glucocorticoid secretion from the adrenal cortex [22]. Endocrine active CRH is co localized with arginine-vasopressin. Ovine CRH is a peptide that consists of 41 amino acids [50]. CRH is released by axon terminals that project to the median eminence and is transported by the hypophyseal portal system to the anterior pituitary, where it induces the synthesis of adreno-corticotrope-hormone (ACTH), ß-endorphine, ß-lipotropin, and alpha-melanocyte-stimulating-hormone/ alpha-melanotropin [2]. ACTH activates adrenal cortex resulting in an increase of glucocorticoids. CRH not only activates the hypothalamic-pituitary-adrenocortical stress-response system, it also has a neurotransmitter function in the brain. Projections to brainstem and spinal cord activate autonome nervous system [47]. Experimental data showed evidence for the participation of CRH-synthesizing neurons in hypothalamus and medullary catecholaminergic neurons in the central organization of responses to audiogenic stress stimuli [23] and intraventricular administered CRH elevates plasma catecholamine concentration and increases arterial pressure and heart rate [19]. CRH receptors have been identified also in brain areas involved in cognitive function as well as in limbic areas [13]. Further more CRH neurons in the paraventricular nucleus and ventromedial hypothalamic nucleus are an important mediator for leptin that contribute to regulation of feeding, adiposity, and expression of uncoupling protein [33]. Results of animal models suggest that growth hormone secretion induced by opioid peptides via GABAergic mechanisms is mediated, at least in part, by hypothalamic GRH [34].

The effects of CRH are transferred by two specific receptors linked with protein G: CRH-R1 and CRH-R2. CHR-R1 receptors are nearly solely expressed in the frontal cortex, the cholinerg basal forebrain, the cholinerg nuclei or brainstem, colliculus superior, basal lateral nucleus amygdala, cerebellum, nucleus trigemini, and anterior pituitary lobe. CRH-R2 receptor predominates in paraventricular neurons, lateral septum, central and medial parts of nucleus amygdalae, and serotoninerg nucleus raphe. Mixed expression of receptors is found in the bulbus olfactorius, hippocampus, stria terminalis, and the periaquaeductal grey [6]. Extracerebral CRH receptors were detected in placenta, myometrium, decidua, and fetal membranes. The presence of CRH receptors was also demonstrated on resident macrophages and on endothelial cells. CRH receptor 1 mRNA was detected in all tissues investigated by RT-PCR, whereas CRH receptor 2 mRNA was restricted to myometrium and deciduas [55]. The CRH 1 receptor plays the most critical role in mediating the ACTH response to shocks, alcohol and lipopolysaccharide, whereas the influence of CRF(2) remains subtle [40].

CRH release of the HPA axis is regulated by different pathways. Corticosterone appears capable of interacting with at least two different neuronal mechanisms to regulate CRH mRNA levels: one is clearly seen in paraventricular neurosecretory neurons, where increasing plasma corticosteroid reduces CRH mRNA levels; the other, seen in neurons in the central nucleus of the amygdala, acts to increase them. Although feedback regulation of hypothalamic neuronal activity by peripheral steroids is a well-established tenet of endocrinology, data show modulation of the intrahypothalamic actions of CRH by adrenal and sex steroids. Circadian influences play also an important role in organizing homeostatic processes, and they have an influence on CRH gene expression too [1, 30, 42, 52].

Different peptides as argenine-vasopressin activate the HPA system. In human beings atrial natriuretic peptide (ANP) is the only neuromodulator with antianxiety effects that inhibits HPA activity at multiple levels. The myocytes of the atrium produce ANP. But it is also found in different brain regions. Pro-ANP plasma levels are independently and inversely related to anxiety. Even in severe coronary hat failure with severely compromised quality of life, anxiety tends to decrease with high pro-ANP levels. This might be part of a negative feedback loop limiting psychological distress [24]. ANP causes a dose-dependent inhibition of CRH-41 release from the rat hypothalamus in vitro [28] and may perhaps be functionally significant cortico-

trophin-release inhibiting factor [18]. CRH-stimulated ACTH and cortisol secretion is significantly reduced by the administration of ANP in comparison to saline. Tis supports the view that ANP may also be involved in the frequently observed nonsuppression after dexamethasone during depression [48]. So physiological stimuli present to be a complex mixture of humoral and neural signals to the CNS, integration of these signal types is the most critical aspect of peptide metabolism [11, 31, 49]. Over a longer time administered CRH and vasopressin in animal models regulate mineralocorticoid and glucocorticoid receptors in hippocampus and anterior pituitary. This reveals another important function of CRH and vasopressin, which could be relevant to understand stress adaptation [27].

Two steroid receptors transfer corticoid level into cell/metabolism activity: the glucocorticoid und the mineralocorticoid receptor. The mineralocorticoid receptor has a 10 fold higher activity than the glucocorticoid receptor and is responsible for the tonic and basal activity. The glucocorticoid receptor is activated circadian and is responsible for the stress response [12]. The main negative feedback regulation of hypothalamic neuronal activity and ACTH release is performed by peripheral steroids. The steroid hormone effect may be classified into two different actions: effects on the genome and effects on membrane receptors [47].

STRESS AND IMMUNOLOGIC SYSTEM

Evidence for interactions between the nervous and immune systems arises from a number of experimental observations: the behavioral conditioning of immune responses, the effects of stimulation or lesion of brain sites on immune system function, the effects of stressors on immune responses and tumor growth, and physiological and neurochemical changes in the brain during immune responses. The links between the nervous and immune systems include glucocorticoids secreted from the adrenal gland, catecholamines and neuropeptides secreted by sympathetic terminals and the adrenal medulla, certain pituitary and gonadal hormones, and polypeptides produced by cells of the immune system. The effect of glucocorticoids is not exclusively immunosuppressive, nor is it adequate to explain all the effects of stress. Human macrophages are stimulated in vitro to phagocytosis by adrenaline/noradrenaline (alpha-receptor) but not by glucocorticoids at physiological levels. High levels of glucocorticoids inhibit phagocytosis [53, 54].

The effects of opiates on immune function are complex; in vitro, endogenous opiates most often facilitate immune activity, but in vivo, opiates appear to inhibit immune responses and impair tumor rejection. The in vitro effects are rarely prevented by naloxone pretreatment and appear to require the integrity of the C- rather than the N-terminal of beta-endorphin, suggesting a nonopiate character. Infections or the administration of antigens increase circulating concentrations of glucocorticoids and activate cerebral catecholaminergic metabolism, especially in the hypothalamus. These responses suggest that challenges to the immune system are physiologic stressors. Interleukin-1 (IL-1) produced by immune cells may be the mediator of these effects, thus acting as an “immunoneurotransmitter”. The cerebral responses suggest that the brain can monitor the progress of immune responses. IL-1 and the glucocorticoids together may form a regulatory feedback mechanism for immune responses [16]. Acute stress also leads to mast cell-dependent serum IL-6 increase that may help explain stress-related coronary inflammation [26].

CRH has also been found in diverse inflammatory sites, the myometrium, the endometrium, and the placenta. Traditionally, hypothalamic CRH has been considered to act indirectly in an anti-inflammatory fashion, since the end product of the hypothalamic-pituitary-adrenal axis is cortisol, a well-known anti-inflammatory compound. However, CRH produced at peripheral inflammatory sites may participate in an auto-/paracrine stimulation of inflammation. CRH in inflammatory sites seems to be involved in the activation of the Fas/Fas ligand system. Furthermore, locally produced embryonic and endometrial CRH plays a role in both the aseptic inflammatory process of implantation and the anti-rejection process that protects the fetus from the maternal immune system. There are two types of G protein-coupled CRH receptors, type 1 and 2. Pyrrolopyrimidine compounds, such as antalarmin, have been developed as CRH receptor antagonists. The systemic administration of antalarmin blocks pituitary CRH receptors and the CRH-induced secretion of adrenocorticotropin [29].

Under conditions of frequent exposure to acute stress and/or chronic, long-term exposure to stress, the LHPA axis becomes dysfunctional and in the process frequently overproduces both CRH and glucocorticoids, which results in many mild to severely toxic side effects. Bidirectional communication between the LHPA axis and immune/inflammatory systems can dramatically potentiate these side effects and create environments in the CNS and periphery ripe for the triggering and/or promotion of tissue degeneration and disease [32].

STRESS AND DEPRESSION

Mood and anxiety disorders are highly prevalent psychiatric disorders, especially in women, and they are associated with significant morbidity and mortality. A considerable literature indicates that vulnerability to depression and anxiety disorders is markedly increased by childhood abuse, e.g., physical, sexual, and psychological abuse, as well as adulthood stressors, e.g., death of a spouse. Recent research on the effects of adverse early life experiences on central nervous system (CNS) stress systems has provided a greater understanding of the link between childhood

abuse and susceptibility to mood and anxiety disorders. Specifically, early life traumatic events, occurring during a period of neuronal plasticity, appear to permanently render neuroendocrine stress response systems supersensitive. These physiological maladaptations likely represent long-term risk factors for the development of psychopathology after exposure to additional stress [37]. The cardinal clinical manifestations of major depression with melancholic features include sustained anxiety and dread for the future as well as evidence of physiological hyperarousal (e.g., sustained hyperactivity of the two principal effectors of the stress response, the corticotropin-releasing-hormone, or CRH, system, and the locus ceruleus-norepinephrine system (LC-NE)). Sustained stress system activation in melancholic depression is thought to confer both behavioral arousal as well as the hypercortisolism, sympathetic nervous system activation, and inhibition of programs for growth and reproduction that consistently occur in this disorder. Data also suggest that activation of the CRH and LC systems in melancholia are involved in the long-term medical consequences of depression such as premature coronary artery disease and osteoporosis, the two-three-fold preponderance of females in the incidence of major depression, and the mechanism of action of antidepressant drugs. In addition, recent data reveal important bidirectional interactions between stress-system hormonal factors in depression and neural substrates implicated in many discrete behavioral alterations in depression (e.g., the medial prefrontal cortex, important in shifting affect based on internal and external cues, the mesolimbic dopaminergic reward system, and the amygdala fear system). Many data indicate that the hypersomnia, hyperphagia, lethargy, fatigue, and relative apathy of the syndrome of atypical depression are associated with concomitant hypofunctioning of the CRH and LC-NE systems.

Disturbances in the HPA-axis have an influence of affective state and cognition. Figure 2 shows a model of interrelation between HPA-axis and behavioural status. In affective disorders a number of neuropeptides seem to be causally involved in development and course of illness, especially corticotropin releasing hormone (CRH), vasopressin and substance P, whose receptors are now targeted with small molecules designed to reduce depressive and anxiety symptoms. CRH appears to play an important role in regulating key neural systems involved in controlling mood, anxiety, feeding behavior, and the interactions between stress and drug addiction. CRH-expressing cells and their target neurons possessing CRH receptors (CRH R1 and CRH R2) are distributed throughout the limbic system. results of several investigations indicate that CRH R1 regulation involves both occupancy of this receptor by its ligand, as well as "downstream" cellular activation and suggest that stress-induced perturbation of CRH-CRH R1 signaling may contribute to abnormal neuronal communication after some stressful situations [4, 20, 38]. Although not exactly neuropeptides, also neurotrophins, may have a distinct role in antidepressant action and possibly also in causation of depression. Schizophrenia-like symptoms are

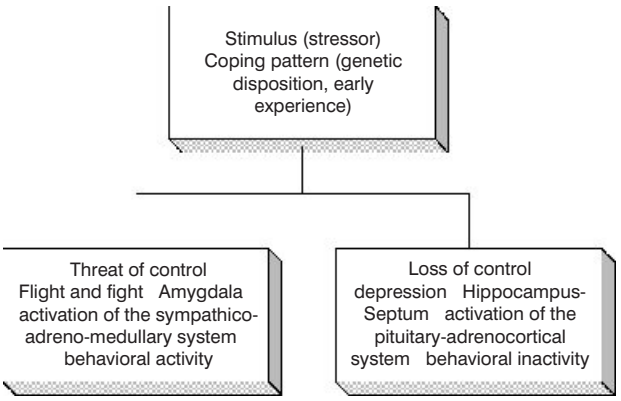

Figure 2. **Coping and predictability concept for stress control and depression** (modified: Borell 2001)

caused by neurotensin (NT), supporting the notion that drugs interfering with NT system are potential antipsychotics [9, 15, 25]. CRH has an anxiogen effect in animal models [17].

CRH ratio also results in changes of sleep-endocrine activity. It is thought that the change of this ratio in favour of CRH contributes to aberrations of sleep during ageing and depression (shallow sleep, blunted GH and elevated cortisol). There are hints that CRH promotes rapid eye movement sleep (REMS) [45]. 50–60% of the patients with major depression showed only low changes of basal, non stimulated levels of ACTH and cortisol. Analysis of circadian peeks resulted in more peeks and higher levels than in healthy people [14]. Increased adrenals as an indication to chronic hyperactivity were found in patients with major depression [41]. This data suggest that CRH overdrive and cortisol overproduction may play a pathogenic role in the occurrence of certain types of depression, directly and/or indirectly, i.e. by induction or exacerbation of disturbances in monoaminergic transmission [51].

THERAPEUTIC PERSPECTIVE

These data indicate the possibility for an entirely different therapeutic strategy than that used in melancholia for the treatment of atypical depression, and they suggest that this subtype of major depression will be associated with its own unique repertoire of long-term medical consequences. Some antidepressant drugs can directly influence corticotropin-releasing hormone (CRH) gene expression. Imipramine and fluoxetine, but not tianeptine, inhibit the human CRH gene promoter activity [5]. CRH-R1-deficiency results in reduced hypothalamic-pituitary-adrenocortical axis activity, in enhanced synthesis of serotonin during basal conditions, and in an augmented response in extracellular levels of serotonin to stress. These data provide further evidence for the intricate relationship between corticotropin-releasing hormone and serotonin and the important role of the CRH-R1 herein [36]. The recent development of selective, small molecule CRH R1 receptor antagonists, which block the effects of CRH both in vitro and

in vivo, suggest that these compounds may be effective in the treatment of affective and anxiety disorders. Early evidence indicates that these agents possess anxiolytic and antidepressant activity in animal behavioral models [10, 21, 35, 46]. Another therapeutic possibility are drug which reduce cortisol secretion [47].

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STRESO IR DEPRESIJOS NEUROENDOKRINOLOGIJA

Santrauka

Streso sąvoką pradėjo vartoti ir šio fenomeno apibrėžimą pateikė Walter Canon 1914 m. ir Hans Selye 1936 m. Normalus neuroendokrininis atsakas į stresą – tai organizmo adaptacijos mechanizmas įvairiems vidiniams bei išorinės aplinkos veiksniams. Svarbiausi stresinės sistemos komponentai – kortikotropiną atpalaiduojantis hormonas ir melsvojo branduolio-noradrenalino-autonominė sistema bei jų efektoriai, pagumburio-hipofizės-antinksčių sistema, autonominės nervų sistemos limbinė dalis. Kortikotropiną atpalaiduojantis hormonas veikia dviejų tipų specifinius receptorius, susijusius su proteinu G: tai CRH-R1 ir CRH-R2. Pagrindinę slopinamąją pagumburio neuronų reguliaciją grįžtamojo ryšio principu atlieka periferiniai steroidiniai hormonai. Pagumburio-hipofizės-antinksčių sistemą aktyvuoja įvairūs peptidai, pvz., argininas-vazopresinas. Žmonių organizme vienintelis neuromoduliatorius, pasižymintis anksiolitiniu poveikiu ir slopinantis pagumburio-hipofizės-antinksčių sistemos aktyvumą įvairiuose lygiuose, – tai prieširdžių natriuretinis peptidas. Straipsnyje aptariami nervų sistemos ir imuniteto sąveikos aspektai. Pagumburio-hipofizės-antinksčių sistemos pusiausvyros sutrikimas turi įtakos afektinei būklei ir kognityvinėms funkcijoms. Kortikotropiną atpalaiduojantis hormonas atlieka svarbų vaidmenį, reguliuodamas NS sritis, kurios dalyvauja nuotaikos, nerimo, maitinimosi, elgesio kontrolėje, daro įtaką patogeneziniam ryšiui tarp streso ir piktnaudžiavimo medikamentais. Pastaruoju metu atrastos selektyvios mažos masės molekulės – CRH-R1 receptorių antagonistai, blokuojantys šiuos receptorius *in vivo* ir *in vitro*. Šios medžiagos gali tapti efektyviais vaistais afektiniams bei nerimo sutrikimams gydyti.

Raktažodžiai: stresas, depresija, pagumburio-hipofizės-antinksčių sistema, kortikotropiną atpalaiduojantis hormonas, prieširdžių natriuretinis peptidas