# STRESS AND COPING

**Richard Rokyta and Anna Yamamotova**
*Charles University, 3rd Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic*

**Keywords:** ACTH, behavior, cognitive appraisal, cortisol, CRH, endocrinology, epinephrine, gluconeogenesis, habituation, hippocampus, hypothalamic-pituitary-adrenal axis, hypothalamus, limbic system, post-traumatic stress disorder, sensitization, stress, stress-induced analgesia, sympathetic-adrenal-medullary axis.

**Contents**





**Summary**

Stress is one of the most widespread biological and psychological phenomena that have been studied in the last century. Hans Selye described it as a nonspecific adaptation reaction to stressful stimuli. At the present time the specificity of the stress reaction is postulated as a psychobiological complex. Since the time of Selye the basic features associated with stress are still valid i.e. alarm reaction, resistance and exhaustion. We already know the molecular and cellular basis of stress reactions as well as the structures responsible for the triggering and maintenance of stress. Therefore we can

describe the anatomy of stress, especially two axes—hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary. We also know the sequence of stress hormones, which are produced during the different stages of stress and which are probably responsible for such events as stress-induced analgesia and other adaptive diseases. For the understanding of the mechanism of stress, it is necessary to take into account age, gender and inter-individual differences. Unfortunately the consequences of acute or chronic stress are very severe, and we are speaking about stress disorders. The main examples are gastrointestinal ulcers, cardiovascular diseases (angina pectoris), immune diseases and psychiatric disorders. Fortunately the defense and coping mechanisms are known and used in medical practice.

## 1. Introduction

The function and integrity of the organism is regulated via homeostatic mechanisms continuously controlling the state of the internal environment to sustain physiologically acceptable conditions. In case the organism is exposed to extreme conditions demanding increased needs of metabolism, a regulatory system must exist to control these functions. This is represented by stress as a complex adaptation response of the organism to the state of actual or potential danger of the subject. A temporary disbalance of previous homeostasis is at that moment more useful than sustaining its stability at any price.

Hans Selye, whose longtime work was devoted to the study of stress, defined it as a nonspecific reaction of the organism to the influence of most of the various exogenous factors that must be faced. A stressor may thus be any stimulus inducing adaptation mechanisms necessary for sustaining homeostasis. Besides physical stressors such as heat, cold and intensive sound it is possible to point out many psychological stressors, and their combinations such as immobilization stress, isolation stress, emotional stress, states of helplessness, hunger, and also anticipation of stressful events. It includes different situations such as illness, examinations, family tragedies, and the effort to exert maximal result in sporting competition. Stress is a significant part of everyday life, but its role is not necessarily always negative. It promotes adaptation because mild chronic stress increases resistance and makes it easy for a person to deal later with complex and/or powerful stress. Nevertheless, long-lasting and intensive stress may be dangerous for the organism. Many negative life events including a strong emotional element (e.g. divorce, death of a close person, retirement, uncontrolled catastrophes) may weaken the adaptive abilities to such an extent that, after a certain period, organ damage, psychosomatic or psychiatric diseases occur.

Positive, productive stress-increasing resistance of organisms is called eustress, whereas negative, harmful stress is called distress.

## 2. General adaptation syndrome

Stress, understood physiologically as a general adaptation syndrome, may be divided into three phases.

### 2.1. Alarm reaction

The first phase is alarm reaction (also called as “fight or flight” response) accompanied by co-activation of the sympathetic-adrenal-medullary system and hypothalamic-pituitary-adrenocortical axis, but the influence of the sympathetic nervous system remains dominant. Activation of the sympathetic nervous system is part of the activation of noradrenergic neurons in the central nervous system, mostly in the posteromedial area of the hypothalamus, where the superior center of the sympathetic system is located and in locus coeruleus of the brain stem. Therefore the catecholamine stress component includes both epinephrine and norepinephrine secretion from the adrenal medulla as well as norepinephrine secretion of the sympathetic and central noradrenergic neurons and also of some neuropeptides such as enkephalins or neuropeptide Y. Via the alarm reaction the organism mobilizes the energetic reserves for immediate utilization, especially for the activity of the nervous system, muscle activity and heart activity. On the other hand, the activities of the digestive system, excretory and reproduction system are significantly suppressed.

### 2.2. Resistance

In the second phase, the phase of resistance, the nervous, hormonal, and immunological mechanisms capable of facing stress for longer period are mobilized. The activation and release of the hypothalamic corticoliberin (corticotropin-releasing hormone, CRH) but also thyreoliberin (thyreotropin-releasing hormone, TRH), and somatoliberin (growth hormone-releasing hormone, GHRH) stimulate the synthesis of adrenocorticotropic hormone (ACTH), thyroidstimulating hormone (TRH) and growth hormone (GH). ACTH stimulates the synthesis of corticosteroid hormones in the adrenal cortex, especially that of cortisol. The specific role of the above-mentioned hormones is to stimulate glycogenolysis, neoglucogenesis, triacylglycerols catabolism and synthesis of ATP. This resistance phase helps the body resist the influence of the stressor for a protracted period. As it runs its course, all the above-mentioned functions gradually normalize.

### 2.3. Exhaustion

As soon as the stress stops, the functions of the organism return to their original state. Only in the case of prolonged influence of the stressor, may a third phase be activated—the phase of exhaustion when the adaptation capabilities are diminishing, the resistance is missing, depletion of hormones occurs and the homeostatic processes are disturbed. This phase is represented by numerous pathological changes in the organism. The pathological changes may occur as a consequences of two different mechanisms: either the stressor does not evoke adequate changes at sufficient speed and intensity, i.e. the adaptation mechanism works with certain latency and persists when is not necessary, or the stress response persists too long even after the end of the stress.

## 3. Anatomy of stress and physiological mechanisms

### 3.2. Hypothalamic-pituitary-adrenal axis

The triggering zone of each stress response is an activation of paraventricular and supraoptic nuclei of the hypothalamus producing corticotropin releasing hormone

(CRH), vasopressin, and oxytocin. While the afferentation of the supraoptic oxytocin neurons is relatively poor and includes the non-painful somatic and visceral afferentation and descendent afferentation from the structures of the limbic system mostly, for CRH release, this afferentation includes all sensory modalities including the transmission of pain. Via processing of the stress stimulus a cascade of events begins based on gradual activation of the hypothalamic-pituitary-adrenocortical axis. Basically, this includes coactivation of two different mutually interacting systems: hypothalamic-pituitary-cortisol system and sympathetic-adrenal-medullary system.

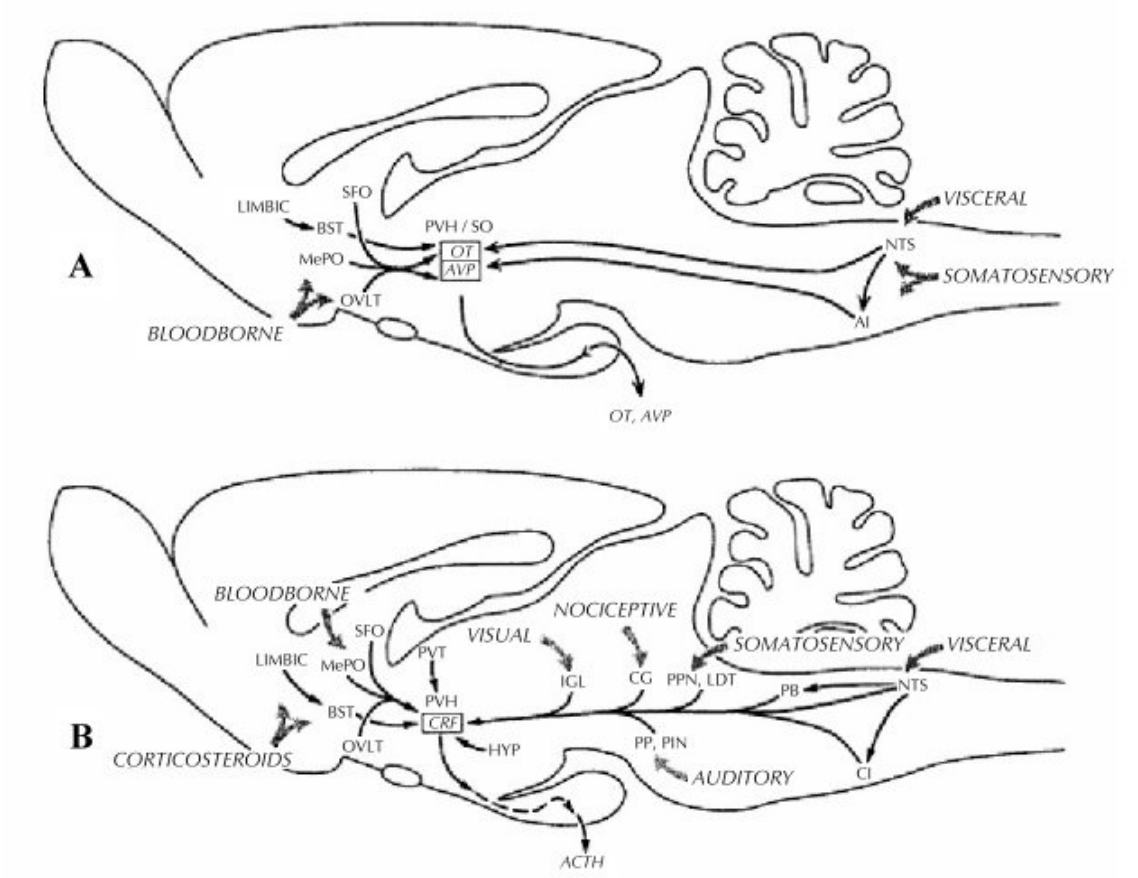


Figure 1. Brain structures responsible for the non-stress (A) and stress (B) effects after the activation of different afferent inputs.

### 3.2. Sympathetic-adrenal-medullary axis

The activation of the sympathetic nervous system is a consequence of activation of noradrenergic neurones in locus coeruleus of the brain stem and posteromedial hypothalamus that represents a superior center of the sympathetic nervous system. The principal mediator of the stress response is norepinephrine. A mutual positive feedback exists between the paraventricular nucleus releasing CRH and the noradrenergic locus coeruleus. CRH stimulates the production of norepinephrine and norepinephrine stimulates the production of CRH, nevertheless, both at the same time suppress their own production. Also acetylcholine and serotonin take part in releasing CRH while GABA and opioids inhibit its secretion. In the anterior pituitary gland the CRH

stimulates the production of proopiomelanocortin (POMC) that represents a common precursor of ACTH and beta-endorphin. ACTH stimulates production of corticosteroid hormones in the adrenal cortex, especially that of cortisol in humans and corticosterone in rats.

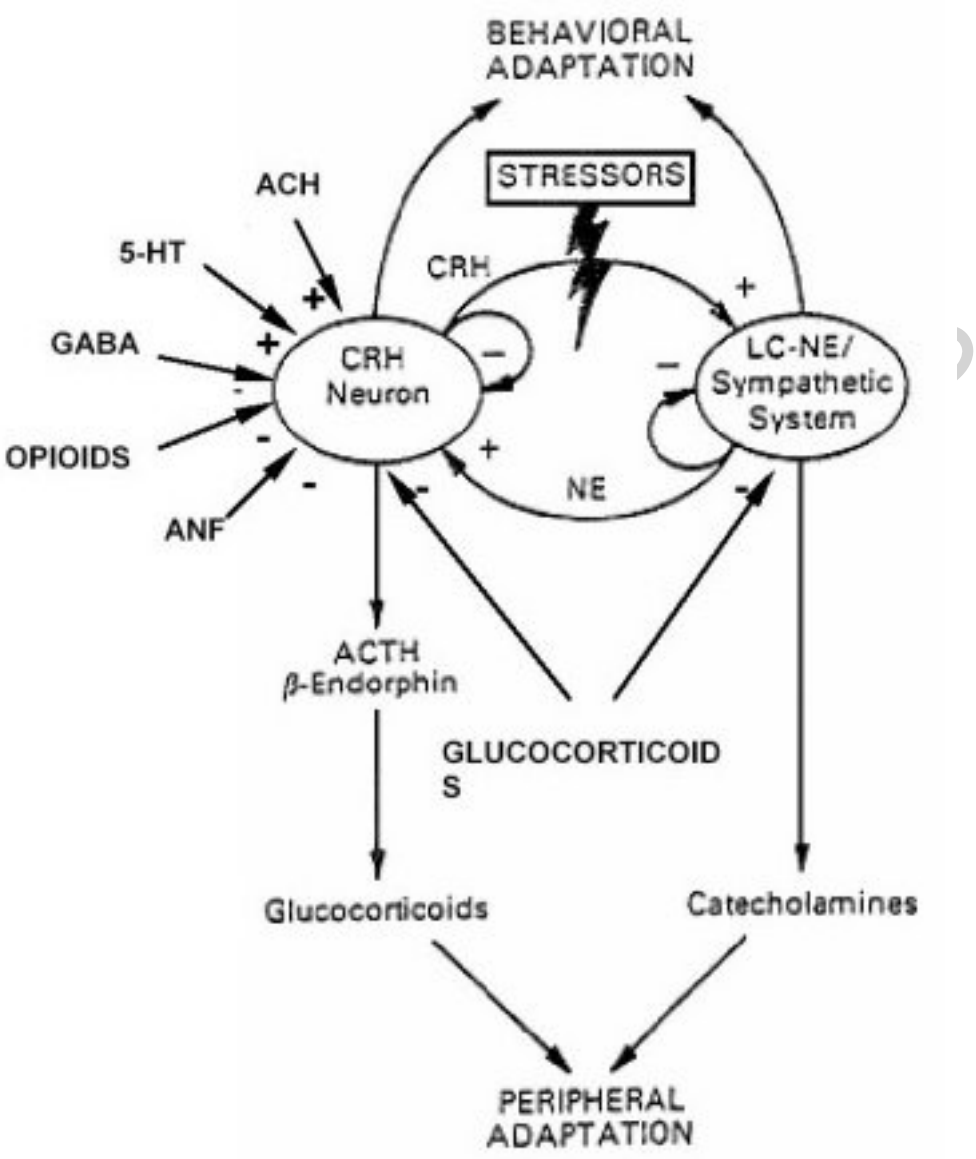


Figure 2. Interaction between hypothalamo-pituitary adrenal axis and sympatho-adrenal system.

### 3.3. Feedback control

The intensity of the stress response is to a great extent dependent on feedback regulatory mechanisms. The classical glucocorticoid (cortisol) feedback depends on the inhibition of the production of ACTH and CRH. It has recently been discovered that cortisol may also inhibit noradrenergic neurons and so weaken their stimulatory effect on the production of CRH. In certain types of stress, the stress response is potentiated by

arginin-vasopressin, which, similarly to CRH, stimulates the production of ACTH. The feedback inhibition is controlled by both a gucocorticoid also a non-glucocorticoid mechanism by the atrial natriuretic factor (ANF) and adrenomedullin. ANF is able to directly inhibit CRH neurons. Adrenomedullin is a peptide produced by the adrenal medulla and vascular endothelium; it decreases the vascular resistance and contributes to the decrease of blood pressure. During stress adrenomedullin inhibits secretion of both cortisol and ACTH.

### 3.6. Stress hormones

The role of epinephrine at stress is to regulate the functions necessary for immediate "fight or flight", i.e. the provision of sufficient amount of oxygen and energy. Therefore epinephrine increases glycogenolysis in muscles and liver while at the same time it inhibits the secretion of insulin and thus limits the transport of glucose to the cells. The increased availability of glucose in blood plasma is then utilized by the nervous tissue. The increasing energetic demands during stress are also covered from the break of adipose tissue. Epinephrine stimulates lipolysis in adipocytes when triacylglyceroles are split to glycerol and fatty acids. Glycerol is utilized in the process of gluconeogenesis and fatty acids serve as energy pool in the process of their oxidation. Positive chronotropic and inotropic effect on myocardium increases the heart frequency, the contractility of myocardium and also the cardiac output. As a result, more blood enters the circulation per unit time. The blood is redistributed in such a way, that preferentially are supplemented muscles while the splanchnic area is less supplied. Because of peripheral vasoconstriction, the perfusion of skin is reduced. The increased need of ventilation during stress is regulated by the bronchodilatatory and vasodilatatory effect of epinephrine in the lungs. To prevent possible blood loss during injury, epinephrine increases haemocoagulation.

Nevertheless, the covering of energetic needs from directly utilizable pools is limited. As a result, during long lasting stress or in later phases of acute stress, secretion of cortisol, the hormone of the adrenal cortex, takes place. It preferentially stimulates the process of gluconeogenesis, when glucose is synthesizes from the catabolism of adipose tissue or proteins. Cortisol exerts a stimulating effect on the catabolism of proteins with the exception of liver tissue, which is the principal place of gluconeogenesis. To make this process more effective, cortisol blocks the uptake of amino acids, but also glucose by the peripheral tissues (its effect opposes that of insulin). A very important property of cortisol is its anti-inflammatory and immunosuppressive effect. Due to its action, a lesser amount of the inflammatory mediators—prostaglandins and leucotriens—are synthesized from their precursor the arachidonic acid. Cortisol affects the amount of circulating leucocytes and also inhibits migration of polymorphonuclear leucocytes and macrophages to the place of inflammation.

Increased production of thyroidstimulating hormone (TSH) during cold stress leads through the hormones of the thyroid gland—thyroxin (T4) and triiodothyronine (T3)—to increased catabolism of carbohydrates and consequently to increased production of ATP. The growth hormone stimulates mainly the catabolism of triacylglycerols and glycogenolysis, i.e. the conversion of glycogen to glucose.

Increased output of vasopressin and aldosterone controls optimal water and sodium balance. Vasopressin (antidiuretic hormone) increases the resorption of water in the kidneys and aldosterone stimulates the resorption of sodium and excretion of hydrogen ions in the kidney, produced as a result of the enhanced catabolic processes. This mechanism opposes a significant decrease of pH. Both hormones contribute to increased blood pressure during the stress reaction and partially prevent the loss of water during bleeding or intensive perspiration.

Prolactin also belongs to stress hormones. Its secretion is influenced by several mediator systems, especially norepinephrine. Norepinephrine acts either directly in a stimulating way on the secretion of prolactin-releasing hormone or is mediated through the activation of the serotoninergic system that on the contrary, inhibits the inhibitory effect of tuberoinfundibular dopaminergic neurons (TIDA neurons) on the secretion of prolactin.

During stress, prolactin stimulates the secretion of cortisol and a possible analgesic effect is expected. Analgesic effect was proved also in oxytocin and in recent years is suspected also in CRH. The analgesic effect of stress hormones may be explained by their mutual interaction with the opioid systems.

### 3.7. Stress-induced analgesia

Stress is a very potent activator of antinociceptive mechanisms. Depending on its intensity, the opioid or nonopioid mechanisms are influenced. Experiments on animals showed induction of opioid analgesia in stress of lesser intensity, while chronic or strong stress induced nonopioid analgesia with the important role of excitatory amino acids and NMDA receptors.

The existence of opioid receptors in the brain may be divided into three functional circuits—nigrostriatal and mesolimbic dopaminergic system, hypothalamic-pituitary axis and descendent antinociceptive system. All three areas are activated during stress, nevertheless the last mentioned plays an important role especially in the modulation of pain. The descendent system of antinociception includes the midbrain, medulla oblongata and the spinal cord. The superior center is the periaqueductal gray (PAG) in mesencephalon. Electrical stimulation, application of morphine or injection of glutamate into this area may induce a very strong analgesia. Neurons from the periaqueductal gray lead to nucleus raphe in the brain stem (nc. raphe magnus, nc. raphe dorsalis) that are the main source of brain serotonin.

The descendent projection fibers of the serotonin neurons create synapses on the neurons of the dorsal horns of the spinal cord where also the axons of sensitive pain neurons end. In the spinal cord, serotonin may inhibit the release of excitatory mediators glutamate or substance P from the sensory endings. Because the serotonin nuclei get afferentation also from collaterals of the spino-reticulo-thalamic pathway, conducting pain, a potential possibility exists that pain might participate in its own inhibition. Nevertheless, this takes place only very rarely, normally in extreme stress situations. This type of analgesia is called stress-induced analgesia.

-
-
-



**Bibliography**

Cacioppo J.T., Malarkey W.B., Kiecolt-Glaser J.K., Uchino B.N., Sgoutas-Emch S.A., Sheridan J.F., Berntson G.G., Glaser R. (1995). *Heterogeneity in neuroendocrine and immune responses to brief psychological stressors as a function of autonomic cardiac activation*. Psychosomatic Medicine 57,154-164. [Brief psychological stressors, heightened cardiac activation, elevated plasma catecholamine concentration and affects on the cellular immune response. The influence is very individual.]

*Encyclopedia of stress* (2000), Ed. G Fink, San Diego. [Comprehensive textbook and description of all aspects of stress.]

Fontana F., Bernardi P., Pich E.M., Boschi S., De Iasio R., Spampinato S., Grossi G. (1997). *Opioid Peptide Modulation of Circulatory and Endocrine Response to Mental Stress in Humans*. Peptides 1997,18:169-175. [The releasing of opioids is one of the possible coping mechanisms. The authors describe the inter-individual variability of the influence of mental stress on circulatory and endocrine response.]

Fullerton C.S. and Ursano R.J. (1997). *Post-traumatic Stress Disorder. Acute and Long-Term Responses to Trauma and Disaster*. American Psychiatric Press. [In this book a widespread type of stress—post-traumatic and disaster stress—is treated from several possible aspects of responses of different body systems.]

Pacak K., Palkovits M., Kopin I.J., Goldstein D.S. (1995). *Stress-induced norepinephrine release in the hypothalamic paraventricular nucleus and pituitary-adrenocortical and sympathoadrenal activity: in vivo microdialysis studies*. Frontiers in Neuroendocrinology16, 89-150. [Using the microdialysis technique, the authors received very important results at the cellular level, with application to the regulatory feedback mechanisms between hypothalamus, pituitary and adrenocortical and sympathoadrenal systems.]

Rahe R.H. (1995). *Stress and Psychiatry*. Comprehensive Textbook of Psychiatry, Ed. Kaplan HI, Sadock BJ, Williams & Wilkins 1545-1559. [The application of the stress principles on the etiology and pathogenesis of mental and psychosomatic diseases].

Sawchenko P.E., Brown E.R., Chan R.K.W., Ericsson A., Li H.Y., Roland B.L., Kovács K.J. (1996). The paraventricular nucleus of the hypothalamus and the functional neuro-anatomy of visceromotor responses to stress. Progress in Brain Research 107, 201-221. [Description of neuro-anatomical connections in the hypothalamus and application in systemic stress paradigms in different models of stress. The authors describe also the neurogenic stress and the emotional brain.]

Selye H. (1976). *Stress in Health and Disease*. Boston. [A compendium with a description of the classical concept of stress, supplemented with new findings.]

Stanford S.C. (1995). *Central noradrenergic neurons and stress*. Pharmacology & Therapeutics 68, 297-342. [A review article with a detail description of the role of noradrenergic neurons during stress and its possible role in the treatment of stress-induced disorders.]

Ursin H., Olff M. (1993). *Psychobiology of coping and defence strategies*. Neuropsychobiology 28,66-71. [A survey of coping methods in psychobiology. Also other psychobiological principals are shown like anti-stress stress response, expectancy and activation.]

**Biographical Sketches**

**Richard Rokyta,** Prof. MD, PhD, DSc. Professor of Physiology and Pathological Physiology, Chairman of the Department of Normal, Pathological and Clinical Physiology, 3rd Faculty of Medicine, Charles University, Prague, Czech Republic. He was born in 1938 in Užhorod, Czechoslovakia. He obtained degrees at the Medical Faculty of Charles University, Prague: Plzeň (MD), PhD and Associate Professor of Pathological Physiology, DSc of Normal and Pathological Physiology.

*Research activity*: developmental neurophysiology, physiology and pathological physiology of thalamocortical relationships, central mechanisms of pain, pathophysiology of epilepsy, transplantation of CNS. Publishing activity: 410 publications and scientific communications, SCI 305, 280 scientific lectures in Czech Republic and abroad. *Editorial Boards:* Physiological Research, Archives de Physiologie, Biochemie et Biophysique, Československá fyziologie, Neuro-endocrinology Letters, chief-editor journal Bolest. *Scientific Councils*: 3rd Faculty of Medicine, Charles University, Prague; Faculty of Medicine, Charles University, Plzeň; Institute of Physiology, Academy of Sciences of Czech Republic; Institute of Experimental Medicine, Academy of Sciences of Czech Republic. *Offices:* Board of the Czech Medical Society J.E. Purkyně, Vice-Dean for Science and International Relationships, Faculty of Medicine, Charles University; Vice-Chairman of the Czech Physiological Society. Vice-President of Médecins Francophones Tchéques. International Societies: IUPS, FEPS, IBRO member of the national committee, IASP, Societé de Physiologie - National Secretary for the Czech Republic and Slovak Republic; New York Academy of Sciences, EBRA.

*Congresses organization:* 1982 Praha Réunion Commune Societé de Physiologie – General Secretary; 1990 Praha – President Réunion Annuelle Societé de Physiologie, 1991 Praha - Regional Meeting IUPS – General Secretary, 1998 Praha Joint Meeting The Physiological Society and the Czech Physiological Society – President; 1999 Praha – Second Congress of FEPS – General Secretary, 2003 Praha IV.th EFIC Congress Praha – General Secretary. He received several international and national awards.

**Anna Yamamotová,** PhD, Associate Professor of Physiology was born in 1953 in Trenčín, Czechoslovakia. She obtained the following degrees: 1984 RNDr., Charles University, Prague; 1984 CSc. Czechoslovak Academy of Sciences, Prague; 2003 Doc. (Associate Professor of Physiology) Charles University Prague. She graduated in the Biological Faculty of Lomonosov University, Department of Physiology of Higher Nervous Activity, Moscow. Diploma dissertation work: "The conditioned motor reaction during the different stages of human sleep and its electrophysiological correlates". Then she worked in the Psychiatric Research Institute, Prague, where she defended a dissertation on the theme: "The study of the activation dynamics from the point of view of electrophysiological correlates of behaviour in laboratory rat". Her research interest was "Biological rhythm and activation dynamics in normal and pathological behaviour". From 1985 to 1993 she was working in the Institute of Physiological Regulations of the Czech Academy of Sciences. In 1990 she was visiting scientist in the Affective Disorder Team (under Prof. P. Grof) in Royal Ottawa Hospital, Ottawa, Canada. From 1993 to the present she was Assistant Professor and Associate Professor at the Department of Physiology and Clinical Physiology, 3rd Faculty of Medicine, Charles University, Prague. Her present interest is: common neurobiological mechanisms of pain, stress and food intake.