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REVIEW ARTICLE

Plant adaptogens III.* Earlier and more recent aspects and concepts on their mode of action

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Introduction

The term adaptogen was originally coined in 1947 by N. V. Lazarev, a pharmacologist, to describe the unexpected effects of dibazol (2-benzylbenzimidazol), an arterial dilator developed in France. Dibazol was found to increase the resistance of organisms to stress in experimental studies – "the state of non-specific resistance, SNIR" (Lazarev, 1962). The term stress is used here in the classic sense as defined by Hans Selye as a state of threatened homeostasis. The original definition of adaptogens was as follows:

– the adaptogenic effect is non-specific in that the adaptogen increases resistance to a very broad spectrum of harmful factors ("stressors") of different physical, chemical and biological natures;
– an adaptogen is to have a normalizing effect, that is, it counteracts or prevents disturbances brought about by stressors and
– an adaptogen must be innocuous to have a broad range of therapeutical effects without causing any disturbance (other than very marginally) to the normal functioning of the organism.

Adaptogens, thus defined, constitute a new class of metabolic regulators (of a natural origin) which have been shown to increase the ability of the organism to adapt to environmental factors and to avoid damage from such factors. Adaptogen as a new concept has become more generally recognized during the last 10 years and has recently been used as a functional term by health authorities (FDA, 1998).

It is important to notice that in former USSR the research on adaptation took a new direction more than 30 years ago. Conventional research on adaptation and stress deals with mechanism of action in situations like high-altitude hypoxia, and physical load training etc., whereas Russian research went on to study mechanism of adaptation in a number of stressful and extreme situations with clear intention to develop methods and pharmacological agents which would help the organism to adapt and cope with such situations.

As a background for the pharmacological research in the area, the Russian scientists used Hans Selye's theory about stress. In 1936, Selye in his experiments on rats found that various harmful influences such as cold, heat, noise, chemicals etc. induce the same "nonspecific" generalized physiological response of the organism (ulceration of the stomach and colon, atrophy of immune system tissue and increase of adrenals) which he named – "stress"** (Selye, 1950).

The stress models used to establish an adaptogenic effect, in vivo were primarily:

– Dynamic and statistical load tolerance
– Stress induced by radiation or sound (vibration)
– Bacterial infection
– Emotional stress

The study of adaptogens developed into a field of biomedicinal research in its own right in the USSR in the early 1960s as the result of two major targeted projects or directions of research. These were: stress research and mapping or screening biologically active substances of natural origin, mainly from the plant kingdom.

If any names would be given in this context two should be mentioned, those of Felix Meerson for his pi-

* Plant adaptogens I. H. Wagner, H. Nörr, H. Winterhoff, *Phytomedicine 1:* 63–76 (1994). Plant adaptogens II. A. Panossian, E. Gabrielian, H. Wagner, *Phytomedicine 4:* 85–99 (1997).

** *Stress,* a term borrowed from physics by W. Cannon and H. Selye, is a state of *threatened homeostasis. Homeostasis* is a complex dynamic equilibrium that is constantly challenged by intrinsic or extrinsic adverse forces or stressors (Cannon, 1935; Selye, 1950; Chrousos and Gold, 1992).

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oneering work on the general mechanism of adaptation: Felix Meerson (Meerson, 1984) and Israel Brekhman (Brekhman, 1968). Meerson suggests how the GABA-ergic system, prostaglandins, natural antioxidants and adenine nucleotides play an important role in such adaptation. Key findings by these scientists are thus:

– a specific adaptation can lead to cross-adaptation (cross-adaptation = non-specific resistance) and that
– there are natural substances which increase the overall capacity to cope with strain/stress of various origins.

The aim of this research was to develop drugs and methods able to stimulate the intrinsic adaptive mechanisms of the organism so as to help it survive in and cope with situations of intense or prolonged stress, while preferably maintaining the capability for physical and mental work.

The first review to be published in the West, covering 15 years of adaptogen research, was presented in the Annual Review of Pharmacology, 1969 (Brekhman and Dardymov, 1969).

A summary written more in the tradition of popular science and with a slightly more limited selection of the factual material is to be found in the article by Stephen Fulder (Fulder, 1980).

Just to give an indication of the extent of the research carried out, it should be said that as early as 1984 there were already about 1.500 studies (mainly pharmacological and clinical) published in Russia concerning extracts or isolates prepared from the plants *Eleutherococcus, Rhodiola and Schizandra*.

Studies performed more recently, primarily in Germany and Japan, have shown a high level of consistency with the results of the Russian research (Nörr, 1993). Studies in the West have, by and large, been directed at certain pharmacological effects. A good example are the recent studies of the protective effects on the liver of the lignans in *Schizandra* against a broad range of toxins and other stressors (Liu et al., 1992; Lu and Liu, 1991; 1992;. Ip et al., 1995; Wang et al., 1994).

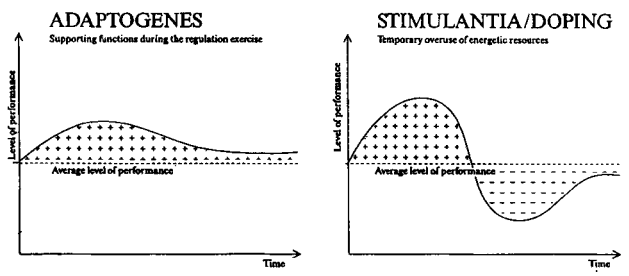

Fig. 1. Difference between adaptogens and stimulants (Qualitative pictures).

The inevitable question presents itself: can the pharmacological effects and investigated biochemical mode of action be explained by a smaller set of assumptions pertaining to the mode of action, and how by a universal and basic principle? In the search for such common cause the most recent development comprises two main areas: molecular biology regarding the protective mechanisms of the cell and biochemistry regarding mediators in the stress systems.

The latest development is to see the adaptogenic effect as an increasing the basal level of dynamic equilibrium *(Homeostasis)* of "switch on" and "switch off" systems. One can thus envisage an increased but balanced basal level of most important mediators of stress system: such as activators NO, PAF and catecholamines and inhibitors such as cortisol and PGE_2.

Another interesting development is some findings in molecular biology which indicate that certain adaptogenic substances can activate the protective mechanisms of the cells linked to increased survival rate in both *in vitro* and *in vivo* experiments. These studies have thus been directed at the formation of certain Heat Shock Proteins (HSP) or "stress proteins" (Malyshev et al. 1997), HSP70 and HSP90 families.

Mode of action – earlier studies

Assuming that adaptogens constitute a novel class of metabolic regulators, the most general question to be answered is: which are the **differences** and **similarities** between adaptogens and known classes of metabolic regulators and other known pharmacological principles? From *in vivo* studies, the ability of adaptogen to increase work capacity has been well established (both in animal and human studies). Therefore it became necessary to determine in what sense an adaptogen would differ from, for example, **stimulants.** Again, from *in vivo* studies, a key difference with respect to the pharmacodynamics was observed. Simply put, this difference is seen in the **recovery process** after exhaustive (physiological load) work. This has more recently been verified in a series of studies in exercised and non-exercised horses (Hancke et al., 1994; 1996). Diagrammatically it can be shown in a qualitative way as in Figure 1.

As mentioned in the introduction, pharmacological studies revealed a basic difference between classical stimulants and adaptogens in situations of forced muscular work. First, stimulants like phenamine give a temporary increase in work-capacity. However after the initial increase there follows a period of marked decrease (with respect to an average level of performance) of the work capacity. In humans, a number of unpleasant side effects appear at this state. Moreover, a repeated application of CNS-stimulants (phenamine etc.)

leads to a decrease in conditioned reflexes, due partly to an exhaustion of brain catecholamines. As a contrast to this overall picture of the pharmacodynamical action of CNS stimulants, extracts and glycosides from the adaptogens *Acanthopanax* and *Rhodiola* displayed a completely different kind of pharmacodynamic action. In particular the level of performance after reaching its maximum is not followed by a corresponding minimum of the average work capacity. For a qualitative picture, see again Figure 1.

A series of experiments, designed to demonstrate this difference between adaptogens and CNS-stimulants **at a more basic, biochemical level,** was undertaken by Brekhman, Dardymov, Galotin and Kindlov in the late 1960s. The general assumption behind the experiments was the hypothesis that the adaptogenic action was dependent **on the cellular synthesis of nucleic acids,** an effect which would be in sharp contrast to CNS-stimulants. In summary these investigation showed that administration of adaptogens, per os, 30 minutes before the test increased work capacity in mice 1.3–1.5 times (swimming tests, climbing tests). Intraperitoneal administration of antitumor antibiotic actinomycin D (150 mg/kg) before adaptogen administration completely eliminated the expected increase in work capacity. The administration of actinomycin alone has no effect on the work capacity of the mice. Since actinomycin D is known to bind to DNA and selectively breaks its ability to serve as a matrix for the synthesis of RNA, the conclusion drawn from these studies was that the **adaptogenic effect was dependent on the DNA-dependent synthesis of RNA** (Dardymov and Brekhman, 1969). It seems however, that **the synthesis of RNA is necessary but not sufficient** for increasing the working capacity.

In another, similarly designed series of studies using i.p. injections of ribonuclease also cancelled the effect of the adaptogens. Ribonuclease itself induces an increase in work capacity. In spite of this the effect of the adaptogens was completely cancelled. The conclusion to be drawn from the latter interpretation of series is less straightforward, as the enzyme ribonuclease is not known to penetrate the cellular membrane. The observed effect could be due to the destruction of cell-surface RNA by the RNAase. It is known that destruction of surface RNA stimulates protein synthesis and hypothetically cell-surface RNA could play a key role in mediating the adaptogenic effect (Malenkov and Kolotygina, 1984).

As this investigation gave credit to the assumption of a **dependence of adaptogenic action on protein synthesis,** a number of further studies were designed in this direction to reveal an eventual **direct effect on protein/nucleic acid production.**

Positive effects on the biosynthesis of proteins and nucleic acids

The investigations aimed to study a modulation of protein/nucleic acid synthesis can be divided into two groups: a) in stress situations, and b) under normal conditions. The following is meant to provide an illustrative selection of performed studies, not to be an exhaustive account.

In stress situations:

DNA-dependent RNA polymerase was inhibited in cell nuclei from skeletal muscles and liver of rats after swimming for 15 min. The inhibition of enzymatic activity was **partly prevented** by an i.p. administration of eleutherosides 45 minutes before swimming. The eleutherosides did not influence the RNA-polymerase activity in vitro (Bezdetko et al., 1973).

Another study showed that 15 minutes of swimming inhibited the incorporation of P^{32} into m-RNA in rat liver nuclei. Normal values of P^{32} incorporation into RNA were recovered only after a 2 h rest. Premedication of rats with eleutherosides intensified two-fold the recovery of m-RNA metabolism (Dardymov et al., 1972).

Li (1969) studied the effect of eleutherosides on the weight and mitotic activity of the regenerating mouse liver. In their experiments two-thirds of the liver was resected and the test group was given eleutherosides 1 h before the operation followed by an administration each on the second and third days after. In a control group of intact mice given the same treatment, no change in weight and mitotic activity in the liver was seen while in the post-operational group a marked increase in both weight and mitotic activity was observed [Li, 1969]. In experimentally-induced cerebral ischemia in rats by constriction of the left cartoid artery the initial reduction of protein was significantly less than in the treated group compared with the control, relative to a higher survival rate in the test group. In line with the above, it was demonstrated in a human study in blood donors that an extract containing eleutherosides stimulated the hematopoiesis. Repeated doses of glucosides isolated from *Rhodiola rosea* increased very significantly the restoration of protein, RNA and free amino acids in the muscles of rats after exhausting exercise (Saratikov et al., 1971).

A number of further studies have been performed along similar lines. To mention a few more: quicker adaptation of erythrocytes to alkaline hemolysis in new born rats which is directly related to the synthesis of the protein part of the hemoglobin molecule (Saratikov et al., 1971), increased restoration of the leukocyte count in rats receiving maximum tolerated doses of ethymidine/cyclophosphane, and increased activity of

the adaptive liver enzyme tryptophan pyrrolase during stress (Leonova and Rodionova, 1979).

Effect on protein/nucleic and synthesis under normal conditions:

Eleutherosides increased the protein synthesis in embryos of sea-urchins. Anisimov and Voropaev (1973) investigated the influence of eleutherosides on the synthesis of proteins in sea-urchins. The activity of total proteins [C^{14}-leucine] increased by 34% in comparison to the control group at the early stage of division between the formation of the second and fourth blastomere). The addition of puromycin to the incubative medium completely cancelled the increase (Dardymov and Khasina, 1972; Anisimov and Voropaev, 1973).

Repeated application of adaptogenic substances (*Rhodiola* and *Eleutherococcus* glucosides) was shown to result in weight gain in young rats, piglets etc. However experiments with young rats (Dardymov and Kirillov, 1965) showed that in contrast to anabolic steroids (testosterone-propionate), the gain in weight was not paralleled by a corresponding increase in the weight of the testicles.

In conclusion it should be mentioned that it still remains unknown the direct molecular targets of adaptogens which are responsible for activation of DNA and protein synthesis during adaptation.

Energetic regulation during stress: increased formation of glucose-6-phosphate

Another series of studies on the mechanism of action of adaptogens were directed on energetic regulation during stress, particularly on increased formation of glucose-6-phosphate. Dardymov and his colleagues performed a number of studies of the influences of adaptogens on energetic regulation during stress. Result of the in experimental work, regarding the biochemical aspects have shown that the studied adaptogens activated the enzyme hexokinase in the glycolysis pathway as follows: glucose → hexokinase → glucose-6-phosphat ↔ pyruvate (via the hexokinase shunt) as can be seen in more detail in Figure 2. The hexokinase reaction is a limiting step in the glycolysis ("bottleneck" reaction). The biochemical studies were proceeded by several investigations on carbohydrate metabolism in animal during stress, with and without the administration of adaptogens. These studies demonstrated a clear insulin-like effect of several of the substances (Dardymov and Khasina, 1972).

It was demonstrated that β-lipoproteins isolated from plasma of stress-exposed or alloxan diabetic animals ones inhibited the glucose uptake by the diaphragms of intact rat. When pretreated with syringin (adaptogen) the inhibition was cancelled. Subsequent

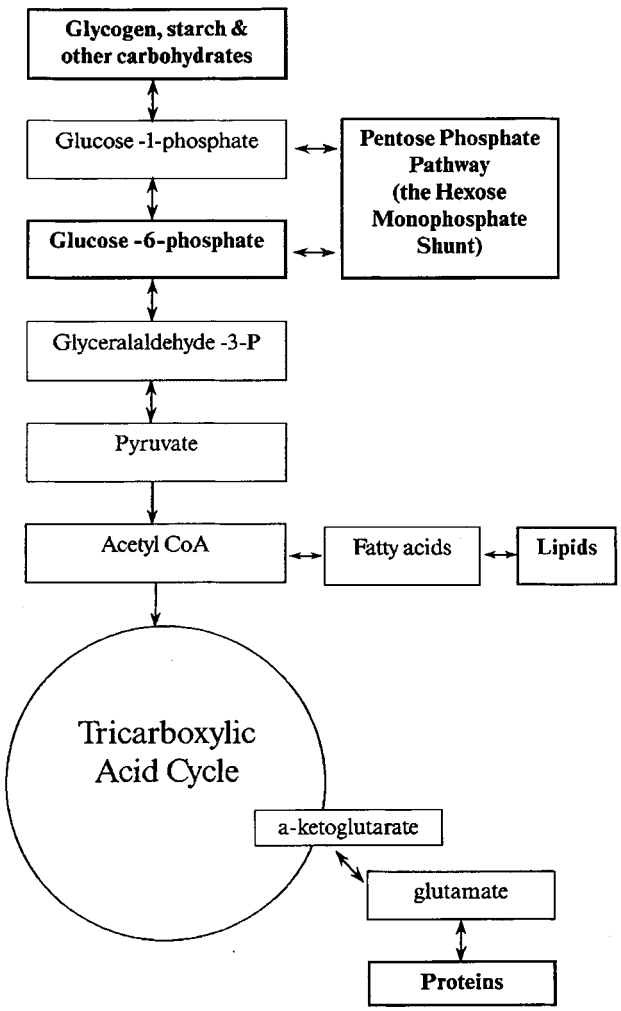

Fig. 2. Glycolysis in pathway associated with lipid and protein metabolism.

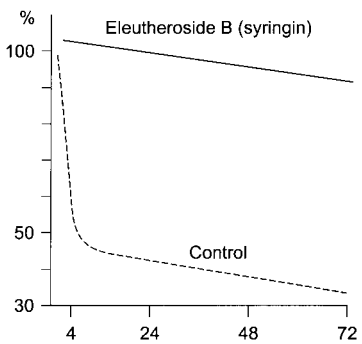

Fig. 3. Effect of stress on hexokinase activity in muscles before and after taking Eleutherosides (I. I. Brekhman Svensk Farmaceutisk Tidskrift, Vol. 83, 3, 127–130 (1978).

in vitro studies showed clearly that syringin (Eleuteroside of *Eleuterococcus*) and other adaptogenic substances were able to cancel the inhibitory action of β-lipoprotein on hexokinase (yeast hexokinase) activity (Dardymov and Khasina, 1972) (see Figure 3).

The enzymatic activity was evaluated by measuring the reduction of glucose and easily hydrolyzed ATP phosphorus (Dardymov and Khasina, 1972) in the incubation medium (24 h). However, it should also be pointed out that syringin (and other eleutherosides) activated the glucogen transport through erythrocytic membranes, both at low and high glucose concentrations (Polukhina et al. 1981). This effect is apparently not related to the hexokinase activity.

It should be emphasized that all these evidences concerning effects of adaptogens on carbohydrate metabolism and energy provision as well as DNA and protein synthesis are rather consequences of their effect on key mediators of stimulus response coupling the cells and regulatory systems, than direct effect on the enzymes involved in these processes.

Limitation of overproduction of catecholamines during stress, catecholamine-O-methyl transferase (COMT)-inhibition

As an example of this approach to study the mechanism of action of adaptogens the hypothesis of their effect on **limiting overproduction of catecholamines during stress** could be mentioned.

A. V. Lupandin and others have focused their attention on the catecholaminergic synaptical modulation of polyphenolic adaptogens exhibiting COMT-inhibitory action during stress. COMT (catecholamino-O-methyl-thansferase = COMT) inactivates catecholamines and an inhibition of this enzyme causes a prolonged activation of adrenoreceptors. A consequence of such a COMT-inhibition is that the catecholamine deposits are not depleted and the release of catecholamines from the nerve-synaptic system is decreased during the general state of stress. It should, however, be pointed out that the hypothesis of a COMT-inhibitory effect is based on indirect experimental data [Lupandin and Lapaev, 1981; Lupandin, 1989; Lupandin, 1991].

Antioxidants/reduction of lipid peroxidation

The development of adaptation to a moderate level of stress entails an increase in lipid peroxidation. As the organism adapts to moderate stress, the degree of the stress reaction gradually becomes weaker and the peroxidation becomes normal. This fact, in combination with the general "peroxidatic stress" by itself has a number of negative consequences for the organism. This leads directly to the question of if, and to what extent, the adaptogens in question display such an effect. The antioxidant effect of the mentioned adaptogens (i.e. those derived from plants of the genera *Eleutherococcus, Rhodiola* and *Schizandra*) is the single most studied mode of action and is also the most verified in recent times outside the USSR/Russia. In particular, a large number of studies have revealed potent antioxidant properties of the *Schizandra* lignans in a number of various models (Liu et al., 1992; Lu and Liu, 1991; 1992; Ip et al., 1995; Wang et al., 1994). It is worth emphasizing that a reduction of lipid peroxidation or antioxidant effects cannot in principle be the main action of the adaptogens, which is evident from the fact that the known strongly antioxidant substances (tocopherols, etc.) do not exhibit adaptogenic properties. Earlier studies of the mode of action of adaptogens can be summarized (oversimplified) in a the schema of Figure 4.

Mode of Action – new concepts

Stress itself is a defence response of the organism, and it may be assumed that antialarm effect of adaptogens would lessen its positive influence on the resistance of the organism. Brekhman, however suggested that adaptogen's induced SNIR is not realized through a general adaptation reaction and is not identical with an enhancement of nonspecific resistance in the alarm stage of stress. SNIR in contrast to the alarm stage of stress, might last long, and function of adrenal cortex at SNIR did not alter (Brekhman and Dardymov, 1969). For a long time this concept was not supported by biochemical evidences on the possible mechanisms of action of adaptogens, which might be one reason, why the notion 'adaptogen' has not gained more attention internationally.

Experimentally confirmed action	Schizandra	Rhodiola	Acanthopanax
Increased synthesis of proteins/nucleic acids		X	X
Increased formation of glucose - 6 - phosphate (activation of hexokinase)		X	X
Catecholaminergic synaptical modulation (COMT - inhibitors)	X		
Antioxidant/reduction of lipid peroxidation	X		

Fig. 4. An overview of some directions of research on the mechanism of action of adaptogens.

During last decades many features of Seleye's defined stress response concept were substantially enriched. By now, the involvement of hormones, cytokines and many other important components of neuroendocrine and immune system in mediating the stress response is well established (Tache and Rivier, 1993). Furthermore, definitions of stress system and stress response were recently update*) (Stratakis and Chrousos, 1995; Kopin, 1995).

There is however a fundamental problem how to harmonize the original definition of an adaptogen with the concepts in modern pharmacology. This becomes clear when we recall two main conditions to be satisfied: an adaptogen should have a **non-specific** action and not cause **disorder in the normal state** of the organism.

This seem to be in clear contrast to some of the key-concepts of modern pharmacology: potency, selectivity and with the efficacy balanced by an accepted level of toxicity.

It is generally agreed that the more selective a drug is the higher is its therapeutical value. This in combination with a high potency is tacitly assumed to lead to an almost inevitable interference with a control system by a restriction of the available strategies of the organism/-cell. Therefore, an updated definition of adaptogen is called for in order to advance towards application in medicine. It is therefore necessary to go into more detail, from a biochemical point of view, how to assess an adaptogenic effect.

What are the mechanisms of action of adaptogens and what biochemical markers can be used for evaluation of the efficiency of adaptogens both *in vivo* and *in virto* experiments on isolated enzyme or/and cell system, animals and humans? How can we biologically and biochemically make standardization? These two basic issues are discussed below.

Stress System, mediators involved in stress response, adaptation and possible mode of action of plant adaptogens

Since adaptogens are considered as substances which adapt organism to stress, studies of their effects on two regulatory systems which are responsible for stimulus response coupling, the immune system and the so called stress-system, are primarily important in understarrding their mechanisms of action.

The stress-system of human beings consists of components of central nervous system (CNS), including corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) neurons of hypothalamic paraventricular nucleus and noradrenergic nuclei of the brain stem, and their peripheral limbs, the hypothalamic-pituitary-adrenal (HPA) axis and the peripheral autonomic system, whose main function is to maintain homeostasis, both in resting and stress states. CRH and AVP neurones and catecholaminergic neurones of the locus ceruleus and other cell groups of the medulla and the pons, are the central coordinators of the stress system, while HPA axis and the efferent sympathoadrenal system (SAS) represent its peripheral limbs. Reciprocal neural connections exist between CRH and catecholaminergic neurons of the CNS.

The SAS and HPA systems are anatomically and functionally interconnected, and during stress they can interact at different levels, e.g. catecholamines stimulate the HPA axis via CRH release, whereas HPA hormones act on the SAS in stress. Recent findings indicate a suppressive effect of endogenous glucocorticoids and a stimulatory effect of chronically elevated glucocorticoid levels on SAS activity during stress. During stress CRH and AVP secretion increases, resulting in increased ACTH and cortisol secretion.

Other factors, such as angiotensin II, cytokines and arachidonic acid metabolites (eicosanoids) are also recruited during the various types of stress. The SAS provides a rapidly responding mechanism that control mostly the acute response of the organism to a stressor. In addition to catecholamines, both sympathetic and parasymphatetic divisions of the autonomic nervous system secrete a variety of neuropeptides, ATP and nitric oxide (Stratakis and Chrousos, 1995).

Figure 5 shows a simplified representation of the components of the stress system, their functional interrelations, and their relations to other systems involved in the stress response (Stratakis and Chrousos, 1995).

Stress itself is a defence response of an organism to external factors (strain), which stimulates formation of endogenous activating messengers, such as catecholamines, prostaglandins (PG), cytokines, nitric oxide (NO), PAF, etc. ("switch on"-system), which in turn activates energetic and metabolic resources of the organism.

For example, NO is produced in large quantities during host defence and immunologic reactions. Because it has cytostatic properties and is generated by activated macrophages, it is likely that it plays a role in nonspecific immunity (Moncada and Higgs, 1993). The NO-dependent vasodilator tone seems to be maintained through the physical activation of endothelial cells by

*) Selye's concept of a single stereotypic syndrome that results from any demand upon the body needs to be modified to reflect differences in the pattern of responses to various stresses. When homeostatic mechanisms do not predominate, the pattern of nonspecific, particularly hormonal, responses may differ among stresses. However, the most demands upon the body, when exceeding a critical level, elicit an array of complex neuroendocrine responses, which may have harmful effects, remains a basic contribution [Kopin, 1995].

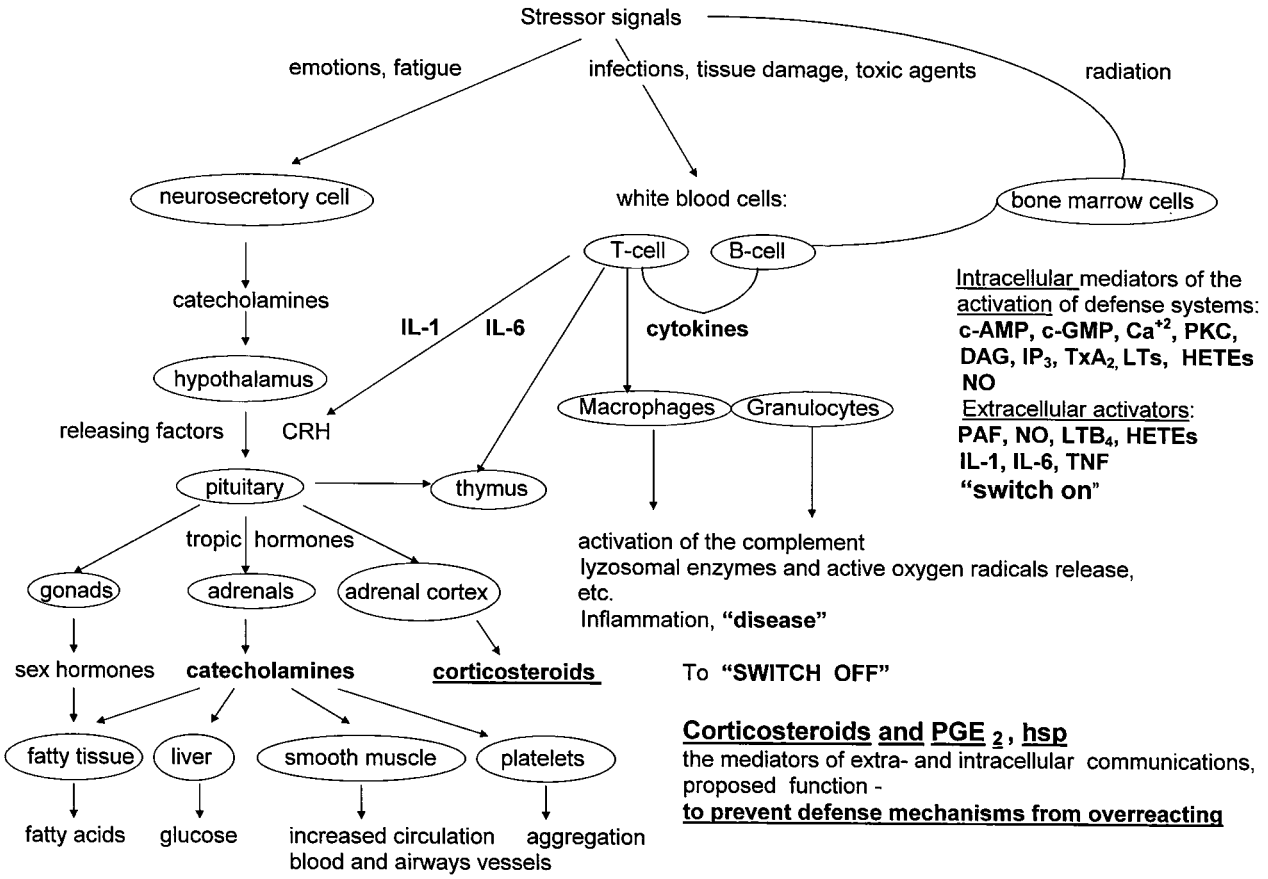

Fig. 5. Components of the stress system and their functional interrelations and their relations to other systems involved in the stress reseponse.

Stress-induced modulation of immune function by the components of CNS and sympathetic nervous system [Friedman and Irwin, 1995] and mechanisms by which peripheral inflammatory mediators may signal the central nervous system (Stemberg and Licinio, 1995). Activation of hypothalamus-pituitary-adrenal (HHA) axis induces various effects on target tissues including fatty tissue, liver, smooth muscle tissue, platelets, etc. Activated immunocompetent cells also interact with endocrine system activating corticotropin releasing factor (CRF) release and consequently corticosteroids. It is recognized that IL-1 and IL-6 have a direct activating effects on hypothalamic-hypophyseal-adrenal axis. Both cytokines induce the release of CRF (-McCann et al., 1995; Cambronero et al., 1992; Hu et al., 1992; Ohgo et al., 1991). Activation of the immune system induces inflammation and "disease". Intracellular mediators of the activation of defence system are c-AMP, c-GMP, $Ca+^2$, PKC, DAG, IP_3, TxA_2, LTs, HETEs, NO. They "switch" on defence mechanisms. Corticosteroids and PGE_2 are mediators of extra- and intracellular communications. Their proposed function is to prevent defense mechanisms from overreacting (Munck et al., 1984). Corticosteroids are recognized as important regulators in the activation and suppression of immune and neuroendocrine systems (Bowen and Fauci, 1988). An increased secretion of glucocorticoids in response to injury or infection is to prevent defence mechanisms from overreacting and themselves threatening homeostasis (Flower, 1985). To do this, they "switch off" defence mechanisms (including stimulation of cytokines, nitric oxide, leukotriene B_4 and PAF formation which "switch on" the defence system).

stimuli such as pulsative flow and shear stress. NO released from nonadrenergic, noncholinergic terminals may also contribute to the regulation of blood flow and pressure (Rand, 1992).

Corticosteroids, CRF and PGE_2 are endogenous mediators of cellular communications, which protect cells and the whole organism from overreacting to the activating messengers ("switch off" system).

The balance between the activities of the "switch on" and "switch off" systems – "reactivity" – reflects the sensitivity of the organism to stressors and the level of protection against their damaging effects. It seems that

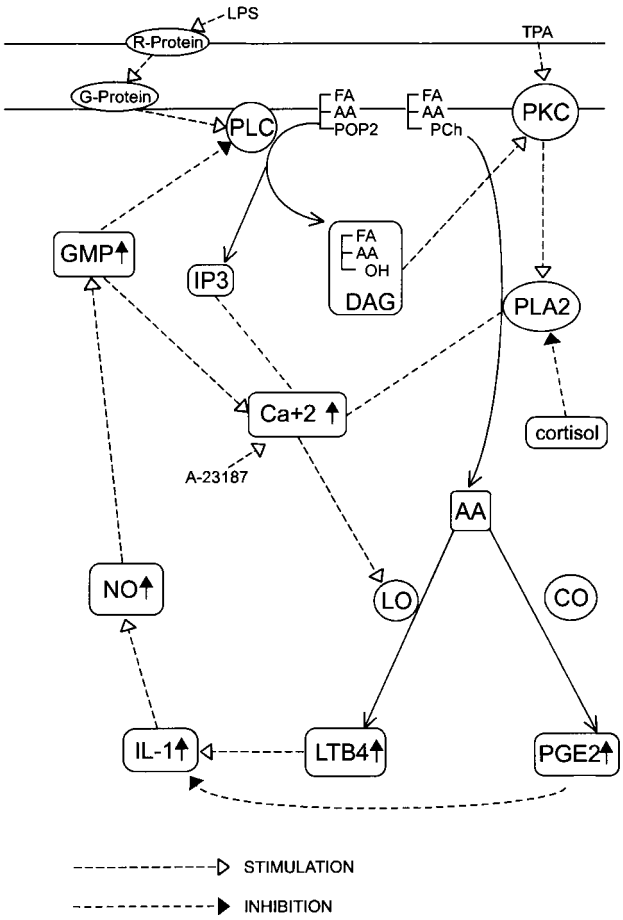

Fig. 6. A proposed model for intracellular signal transduction pathways and involvement of mediators of stress system in stimulus-response coupling.

Upon ligand binding, class II receptors mediate the signal through G family proteins [Barnard, 1992], which are involved in the activation of phospholipase C (PLC) [Helper and Gilman, 1992]. PLC hydrolyses inositol-containing phospholipids, which is then converted to inositol-triphosphate (IP_3) and diacylglycerol (DAG) (Cockroft, 1992). IP_3 diffuses to the cytoplasm and binds to an IP_3 receptor (Barnard, 1992) resulting in calcium release which in turn activates type II and cytosolic type IV phospholipases A_2 (Clark et al., 1991). PLA_2 catalyze the liberation of fatty acids from the *sn*-2 position. DAG binds to the regulatory site of PKC in the cell membrane and activates the kinase, which in turn activates phosphorylation of cytosolic PLA_2. PLA_2 induces synthesis of platelet activating factor (PAF) and arachidonic acid release, (Asaoka et al., 1992) which is metabolized to prostaglandins (PGs) and leukotrienes (LTs). LTB_4 stimulates IL-1α production in LPS stimulated monocytes (Rola-Pleszczynski and Lamaire, 1985). PGE_2 is known to inhibit IL-1α production and therefore suppress certain immune reactions. Inhibition of lymphocyte activity is the main function of PGE_2 in the immune system, and PGE_2 may be viewed as a macrophage messenger transducing an inhibitory signal to lymphocytes (Goodwin and Webb, 1980). IL-1α is known as a potent mediator of inflammation and immune response: it has pyrogenic properties, induces acute-phase reaction, activates granulocytes, eosinophils, natural killer, T- and B-cells, reactive oxygen intermediate and nitric oxide production, etc. (Durum et al., 1985). IL-1α is known to increase PLA_2 (-type II) activity (Nakazato et al., 1991) and production of nitric oxide, which interacts with HEME prosthetic group of guanylate cyclase thus leading to increase c GMP levels. Low concentrations of NO is known to activate guanylyl cyclase and elevate cyclic GMP level in cells (Moncada and Higgs, 1993). Corticosteroids, which are known to inhibit AA release (Flower, 1985) are also potent inhibitors of macrophage induced NO production (Di Rosa et al., 1990).

in the process of adaptation to stressor's effects this balance alters and plant adaptogens could be the agents which reduce the damaging effects of various stressors due to alteration in the reactivity of host defence systems.

An excessive basal and/or stress-responsive activity of the stress system is associated with increased arousal or anxiety, increased blood pressure, gastrointestinal dysfunction, and immune suppression (Stratakis and Chrousos, 1995). Both the HPA axis and SAS system appear chronically activated in melancholic depression which is characterized by the hyperarousal (anxiety) and suppression of feeding and sexual behaviors (anorexia, loss of libido), and an excessive and prolonged redirection of energy with tachy- and hypertension – as classic manifestations of the "generalized stress response" (Gold et al., 1988). Chronic activation of HPA axis has been shown also in other conditions, such as anorexia nervosa, panic anxiety, obsessive-compulsive disorder, chronic active alcoholism, alcohol and narcotic withdrawal, excessive exercising, malnutrition, or sexually abused girls (Stratakis and Chrousos, 1995).

On the other hand chronically decreased basal stress-responsive activity of the stress system are associated with decreased arousal, and a suboptimal physical and mental performance and a decreased feeling of well-being. Seasonal depression in the dark months of the year, the postpartum period, the chronic fatigue and fibromyalgia syndromes represent this state under these conditions CRH secretion is decreased and symptoms, such as increased appetite and weight gain, somnolence and fatigue are seen (Chrousos and Gold, 1992).

Stimulus response coupling system responsible for defence and adaptation of organism is a multitarget pharmacological system. Activation of neuroendocrine and immune systems induces various effects on target tissues including fatty tissue, liver, smooth muscle tissue, platelets, etc. Meanwhile, all these cells and tissues

have common mechanisms of activation and deactivation outlined on Figure 6.

It seems unlikely to expect that adaptogens have one or few targets (like antiinflammatory drugs). Moreover the **wide range** of medical indications for which adaptogens have been used and recommended suggests that the active principles of these "universal remedies" are directed towards those regulatory systems which are common for all the tissues involved in the regulation of homeostasis (immune or/and hormonal, CNS). These could be the stress system and extra- and intracellular signaling systems, e.g. eicosanoids and NO. Eicosanoids also play an important role in many regulatory systems: central nervous, neuroendocrine-, immune-, intra- and intercellular communication, cell differentiation and proliferation, DNA synthesis, etc. Corticosteroids block their formation at the level of precursor – arachidonic acid release.

The action of corticosteroids is known to regulate carbohydrate-, lipid-, protein- and nucleic acid metabolism, to mobilize the resources of the organism under stress to increase its resistance to damaging factors (trauma, infection, hemorrhage, etc.), and to decrease the immunoreactivity of the organism (blocking the migration of leukocytes into inflammatory *loci*), etc. (Bowen and Fauci, 1988). The molecular mechanisms of action of corticosteroids are also associated with the biosynthesis of eicosanoids. They inhibit arachidonic acid (AA) release and consequently the biosynthesis of eicosanoids (Flower, 1985).

It is also well known that the physical endurance of an organism, as well as the formation and secretion of corticosteroids, are all increased as a result of its adaptive reaction (Viru, 1981); strong increase of corticosteroid production normally occurs in any stress state. High levels of cortisol in blood of emotionally depressed primates is well documented. Conversely, continuos treatment with corticosteroids suppresses the formation of ACTH, and thus production of endogenous corticosteroids by the adrenal cortex, which in turn increases the hypersensitivity of the organism to harmful stimuli. This physiological relationship has provoked interest in natural stimulators of the hypothalamus-pituitary-adrenal system, such as the plant adaptogens which are devoid of the disadvantages of corticosteroids.

There is plenty of evidence indicating that single administration of an adaptogen activates ACTH and corticosteroid formation, and that subchronic pretreatment with adaptogens normalizes stress hormone levels (Wagner et al., 1994; Panossian et al., 1997; Dardymov, 1976). For example Cucurbitacin R diglucoside, [DCR,16α,20-dihydroxy-2β,25-di(1-O-β-D-glucopyranosyloxy)-cucurbiten-5-trion-3,11,22], one of the active principles of *Bryonia alba* L. roots, which has been found to exhibit adaptogenic activity in preclinical and clinical trials stimulates and the biosynthesis and secretion of corticosterone by adrenal cortex of rats (Panossian et al., 1997). This increase is evidence for the mobilization of resources of the organisms. It is known that the level of corticosteroids increases as a result of a long-time training or adaptation, and that a trained organism has an insignificant response to stress signals due to increased activity of HPA axis. In contrast, the activation of the HPA in the untrained organism is very pronounced (Viru, 1981). DCR's influence is in this case is similar. Stress signals did not have marked effects on the control group after DCR administration even when the level of corticosterone was four fold (Panossian et al., 1997). This is a typical example of stress-protective effect of DCR, that is directly associated with adrenal cortex.

DCR inhibits ACTH-induced corticosterone formation from isolated adrenocortical cells. Thus, DCR stimulates the adrenal cortex. This effect could be compared with the effect of physical training when the resistance of the organism increases to adapt to stress.

Moreover, it has been suggested that these results explain why *Bryonia alba* root, containing DCR as one of the major compound is effective both against diseases, that are treated by stimulating the adrenal cortex (inflammation, allergy, collagenoses, neurodermitis, polyarthritis, asthma, rheumatism, hepatitis, leukemia, gastro-intestinal disorders), and diseases treated by reducing an increased secretion of corticosteroids.

Because DCR is a modulator of corticosteroids secretion, *Bryonia* extract has been recommended for clinical trials of diseases, in which synthetic corticosteroids are the standard treatment (psychiatric disorders, diabetes, ulcers, reduced resistance to infections, pimples). Advantage of DCR is that it mobilizes the secretion of adrenal hormones to optimal levels and protects the adrenal cortex from hypotrophy, which could be side effect of chronic corticosteroid treatment.

DCR prevents stress induced alterations of eicosanoids in blood plasma and moderately stimulates adrenal cortex to adapt organism to stress, since a moderate increase in corticosteroid secretion protects the defence systems of the organism from becoming hyperactive. DCR enhances the sensitivity level to stress due to effects of eicosanoids and corticosteroids. The eicosanoid system is a modulatory system supporting homeostasis (Claude Bernard "homeostatic hormones"; Foegh and Ramwell, 1983). It plays an important role in adaptation processes.

Recent study in athletes demonstrates that stress, namely acute physical exercise activates formation of cortisol and nitric oxide in the blood and saliva (Panossian et al., 1999). Chronic physical exercise increases the basal level of these stress-mediators in blood and

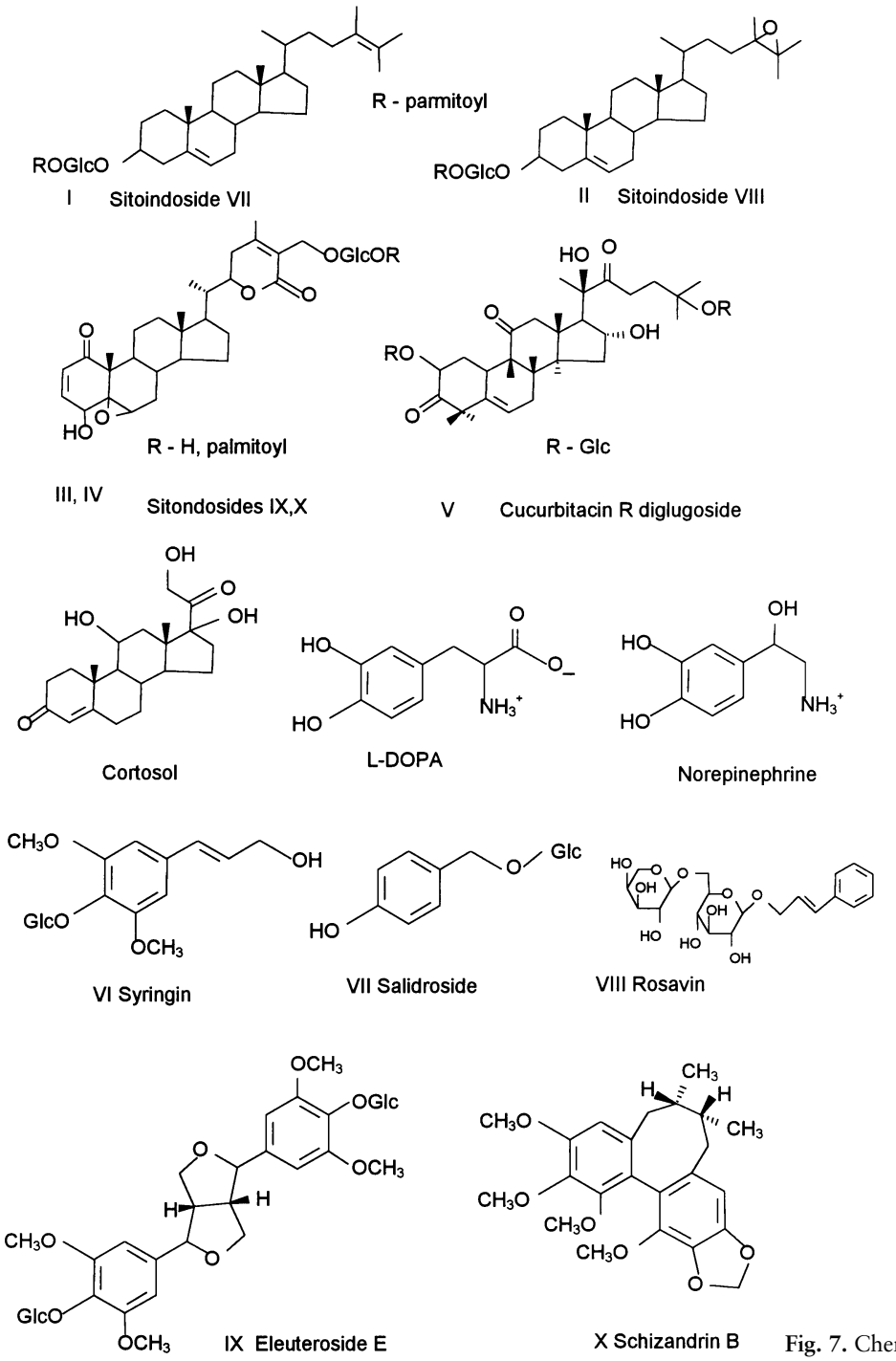

Fig. 7. Chemical structures of compounds I–X.

saliva of well and long trained athletes versus beginners and sedentary subjects. Acute physical loading does not increase the level of cortisol and NO in these athletes. Plant adaptogens, *Schizandra* and *Bryonia* have prostressor effect: they activate formation of both NO and cortisol in blood plasma and saliva, however this activation adapt a organism to further heavy physical loading. Physical exercise does not increase both NO and cortisol level in saliva after the treatment with adaptogens. Their level decreased versus before exercise. Thus, adaptogens increase the production of both activating (NO) and deactivating (cortisol) messengers of stress system. Adaptogens are challengers of defence response of the organism. In other words, adaptogens increase the capacity of stress system to respond to external signals at the higher level of the equilibrium – het-

erostasis (Fig. 8). In subjects, which were already adapted to chronic heavy physical exercise (e.g. well trained athletes) and with basically increased level of cortisol in blood or saliva, physical exercise as well as adaptogens have rather opposite effect on stress – a decrease of the NO and cortisol level, probably due to their increased utilization.

As mentioned above, it is essential to consider and find out the crucial difference and similarity between adaptogens and known classical metabolic regulators and other drugs. We emphasized earlier the difference with respect to CNS stimulants. Now, having gone more into detail regarding the mode of action at a biochemical level, we have seen a number of **similarities** with known substances: corticoid-like action, catecholamine like etc. There is also a suggestive **structural** similarity if one looks at active principles of plant adaptogens as is shown below.

The active principles of plant adaptogens as far as investigated can be divided into two main chemical groups (Fig. 7):

- Terpenoids with a tetracyclic skeleton like cortisol:

Sitoindosides I–IV *(Withania somnifera)* (Bhattacharya et al., 1987; Ghosal et al., 1989

Cucurbitacin R glucoside V *(Bryonia alba)* (Panossian et al., 1997)

- Aromatic compounds, structurally similar to catecholamines

Lignans: Eleuteroside E IX *(Eleuterococcus senticosus)* (Elyakov and Ovodov, 1972) Schizandrin B X *(Schizandra chinensis)* (Kochetkov et al., 1962)

Phenylpropane derivatives: Syringin VI *(Eleuterococcus senticosus)* (Elyakov and Ovodov, 1972: Wagner et al., 1982)

Rosavin VIII *(Rhodiola rosea)* (Kurkin and Zapesochnaya, 1986)

Phenylethane deivatives: Salidrosid VII *(Rhodiola rosea)* (Ssaratikov et al., 1968)

Summary and conclusion

Stimulus-response coupling systems responsible for defence and adaptation of organism to stressors are multi-target and very complicated pharmacological systems, including the neuroendocrine (stress) and immune system. The mode of action of adaptogens is basically associated with the stress-system (neuroendocrine-immune complex) and can be directed on the various targets of the system involved in regulation (activation and inhibition) of stimulus-response coupling.

However, clinical studies performed according to the *most* modern standards are quite limited. On the other hand there is an extensive amount of clinical experience and also established use in self care etc. These aspects are planned to be dealt within a subsequent article which will be devoted to the application in three areas: self care, adjuvants in medicine and curative action in some diseases.

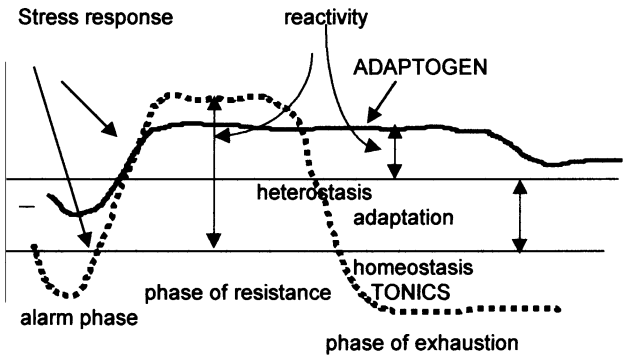

Fig. 8. Stress response and effect of adaptogens.

At this stage, nevertheless, it seems possible to define some most important "stress-markers" for evaluation of efficiency of adaptogens in experimental and clinical pharmacological studies. They can be both activating *(catecholamines, LT-s, cytokines, NO, etc. – "switch on" system – which activates energetic and other resources of the organism),* and deactivating *(corticosteroids and PGE_2-endogenous mediators of cellular communications, which protect cells and whole organism from overreacting to the activating messengers – "switch off" system)* stress-messengers.

The balance between the activities of the "switch on" and "switch off" systems reflects the well being of the organism. It could be established on different levels of the homeostasis (heterostasis) with different levels of the sensitivity to stressors (Figure 8).

The response of stress system – "reactivity" is different at the various levels of heterostasis and depends on adaptation – capacity of the organism (or a cell) to protect itself. In the process of adaptation to stressor's effects the basal levels mediators of switch on (e.g. NO) and switch of (e.g. cortisol) systems are increasing but their balance (the ratio) does not change. In other words, adaptogens increase the capacity of stress system to respond to external signals at the higher level of the equilibrium of activating and deactivating mediators of stress response. Consequently, plant adaptogens can be defined as "smooth" pro-stressors which reduce reactivity of host defense systems and decrease damaging effects of various stressors due to increased basal level of mediators involved in the stress-response. In further studies of adaptogens it seems important to find correlation between adaptogenic activity (a decrease in the "reactivity" of the organism – *the basal level of activating and deactivating messengers: ILs,*

LTB_4, NO, PGE_2, cortisol, but not their ratio) and their therapeutic efficiency (symptomatic evaluation).

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