Introduction
Adaptation response for physical and emotional stimuli in the course of life for its core existence is in general referred to as the stress response. These involve behavioral, neuroendocrine and neurochemical changes. Temporal prolongation of this adaptation to the “stressors” will result in sustained over-activation of several stress systems and may lead to the development of stress-related psychopathologies, which cut across the boundaries of diseases including central and peripheral systems. The objective of the present study is to have an insight into the various components involved in stress response, identify potential therapeutic targets and evaluate lead molecules from plant origin for their therapeutic efficacy.

**Stress response**

Stress is defined as a state of threatened homeostasis, which can be of physical and/or psychological nature. In particular, psychological and social stimuli were found to be powerful ‘stressors’ (Mason, 1971; Koolhaas *et al*., 1997). The stress response is an adaptive compensatory response of the organism to sustain homeostasis. The concept of stress was first described by Selye (1936, 1950). He was intrigued by the non-specificity of the body’s response to stress. Indeed, any perceived stressor would lead to the activation of the autonomic nervous system and of the Hypothalamus-Pituitary-Adrenal (HPA) axis. However, the characteristics of the stressor (such as type, duration, predictability and controllability of the stressor), the effects of the end products of the stress response and individual differences (genetical factors and experience) result in very specific effects of the stress response. Identifying individual differences in stress responses and stressor-specific pathways in brain may be essential for understanding and treatment of the pathogenesis of stress-related disorders. In response to stress, activation of the autonomic nervous system and the HPA axis will subsequently lead to behavioral, physiological and neurobiological adaptations. Initially the stress response will lead to an increase in sympathetic nervous activity. This sympathetic activity results in an increased release of adrenaline (from the adrenal medulla) and nor adrenaline (from other sympathetic nerve endings throughout the body) into the bloodstream. These catecholamines stimulate the heart and increase the blood flow to the central nervous system and muscles within seconds, allowing the organism to directly respond to the stressor by vigilance, arousal, and activation. Activation of the HPA axis results in the secretion of glucocorticoid hormones. Peak levels of these hormones are usually
achieved 10 to 30 min after the onset of the stress response. The primary action of the glucocorticoids is to elevate blood glucose levels. In addition, glucocorticoids are very important to suppress the stress response, to mediate recovery from the stress response and to prepare for the next encounter. Both the neuroendocrine and autonomic systems interact at several levels, and proper functioning of these systems is essential for normal adaptation to stress. In most cases, a brief period of controllable stress can be experienced as excitement and may be beneficial to emotion and health. If, however, the stressor is chronic or uncontrollable, the HPA axis is activated for a prolonged time period. This can lead to a state of hypercorticism and disturbed negative feedback function. In particular, overexposure to corticosteroids may result in changes of neurotransmitter systems such as nor adrenaline, dopamine and 5-Hydroxy tryptamine (5-HT) system by adversely effecting mood and cognition.

**Functional significance of the Hypothalamus pituitary and adrenal (HPA) axis**

The HPA axis is activated during stress but it also coordinates circadian events, such as food intake and the sleep/wake cycle. This diurnal activity of the HPA axis results in a peak of glucocorticoid hormone secretion at the onset of the active period (which is the dark period in night active animals). When the HPA axis is activated during stress or around the circadian peak, corticotropin-releasing hormone (CRH) is produced in neurons within the Para ventricular nucleus (PVN) of the hypothalamus. CRH stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH) into the bloodstream. In the adrenal cortex, ACTH is bound to its receptors and this stimulates the synthesis of glucocorticoids (cortisol in humans, corticosterone in rodents) from cholesterol and increases the subsequent secretion of these steroids into the systemic circulation. For many years, it was believed that these glucocorticoid hormones mainly acted at the level of the peripheral nervous system via binding to intracellular glucocorticoid receptors (GRs), which are found in most peripheral organs. However, this idea was completely changed since the discovery of receptors for stress hormones within the brain. Glucocorticoids easily enter the brain due to their lipophilic nature. Here they can bind to mineralocorticoid receptors (MRs) in addition to GRs (Reul and De Kloet, 1985). MRs are also present in the kidney regulating the salt and water balance of the organism by binding aldosterone rather than glucocorticoid hormone. In contrast with the brain, glucocorticoids in the kidney are metabolically inactivated by the presence of 11β-hydroxysteroid dehydrogenase (11a -HSD) type 2. The MR and GR
differ in their distribution in the brain and in their affinity for corticosteroids. The MR is restricted to ‘limbic’ brain structures (hippocampus, amygdala and septum), whereas the GR has a widespread distribution, and is abundantly expressed in brain regions involved in the stress response such as the hypothalamus, hippocampus, amygdala, various brain stem nuclei and pituitary. MRs has a high affinity for corticosterone, approximately 10-fold higher than GRs (Reul and De Kloet, 1985). As a consequence, MRs are predominately occupied at low corticosterone levels (during basal trough), whereas additionally GRs will become occupied when corticosterone levels are high around the circadian peak and during stress (Reul and De Kloet, 1985). This differential affinity for corticosterone in addition to the differential distribution of the two receptors may indicate that corticosterone has differential functions after binding to the MR or GR. MRs determine the sensitivity of the HPA response and are thought to be involved in evaluating of environmental stimuli, preparing the organism for a certain behavioral response in order to limit homeostatic disturbance as much as possible. Activation of GRs (always in addition to already activated MRs) is needed for the termination of the HPA response, to mediate recovery from stress, to facilitate behavioral adaptation, and to prepare to following stressors (Derjkert et al., 2002).

**Stress and Free radicals**

The brain, under conditions of stress is in a high state of metabolic activity. The “leakage” of high-energy electrons along the mitochondrial electron transport chain causes the formation of superoxide (O$_2^-$) and H$_2$O$_2$ (Coyle and Puttfarcken, 1993).

The production of mitochondrial superoxide radicals occurs primarily at two discrete points in the electron transport chain, namely at complex I (NADH dehydrogenase) and at complex III (ubiquinone-cytochrome c reductase). Under normal metabolic conditions complex III is the main site of ROS production (Turren, 1997). With respect to human ageing the Achilles’ heel of this elegant system lies in the formation of the free radical semiquinone anion species (\(\cdot Q^-\)) that occurs as an intermediate in the regeneration of coenzyme Q. Once formed, \(\cdot Q^-\) can readily and non-enzymatically transfer electrons to molecular oxygen with the subsequent generation of superoxide radical. The generation of reactive oxygen species (ROS) therefore becomes predominantly a function of metabolic rate and, as such, the rate of living can be indirectly translated to a corresponding rate of oxidative stress (Finkel and Holbrook, 2000). When the body is in a state of stress, centrally there is a facilitation of neural
pathways mediating, among other functions, arousal, alertness, vigilance, cognition, and focused attention, as well as appropriate aggression, with concurrent inhibition of pathways that sub serve vegetative functions, such as feeding and reproduction. Peripheral changes occur principally to promote an adaptive redirection of energy. Thus, oxygen and nutrients are directed to the central nervous system and the stressed body site(s).

_Anti-stress agents._

Temporal prolongation of adaptation response during stress full conditions results in various pathophysiological states that cut across the traditional concept of disease and include a range of disorders like hypertension, coronary heart disease (Roy et al., 2001), gastric ulcers (Yadin and Thomas, 1996), immunosuppression (Purett, 2001), metabolic disorders like diabetes (Fitzpatrick et al., 1992), reproductive dysfunction (Dabson and Smith, 2000), mental depression, memory loss and host of other diseases (Gareri et al., 2000). Due to the non specific nature of the stress pathogenesis, a separate class of therapeutic agents was evolved known as “adaptogens”. The term adaptogen was described by Lazarev (1947) as “the substance which can develop a state of raised resistance”, enabling an organism to cope with stressful situations. Therapeutic approach for stress from ancient times has involved utilization of substances from natural origin, rather than synthesis of new chemical compounds. Pharmacological investigations have shown that the basic effect of _Panax ginseng, Eluherococcus senticosus_ and _Rhodiola rosea_, is their ability to increase non-specific resistance of the organism to various untoward influences (Brekhman and Dardymove, 1969). Initial studies on plants originating from folk medicine along with an exponential increase in knowledge regarding the interactions among components of the stress system have encouraged various investigators to evaluate the potential of plant adpatogens for usage in modern day medicine. Further enrichment of the study on plant derived adaptogens was enabled by the substantial work carried out on plants such as _Ocimum sanctum_ (Bhargava and Singh, 1981), _Emblica officinalis_ (Rege et al., 1999), _Bacopa monniera_ (Rai et al., 2003a), _Ginkgo biloba_ (Rai et al., 2003b) and _Withania somnifera_ (Muruganandam and Bhattacharya, 2003) and several other plants whose anti-stress activity was partially evaluated.