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# Stress, Hypertension and Yoga

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## Abstract

Stress and stress-related disorders are emerging as a major health challenge. In the classical stress concept, stress can be broadly defined as an actual or anticipated disruption of homeostasis by certain physical and psychological events that are known as 'stressors'. Prolonged exposure to stress can lead to a destructive, self-perpetuating cascade of neuroendocrine, metabolic and neuropsychological alterations that play an important role in the development and progression of cardio-vascular disease (CVD) like hypertension. Dysregulation of stress system is causally linked to pathogenesis of essential hypertension, which involves over activity of hypothalamic-pituitary-adrenal axis (HPA) and sympathoadrenal system (SAS) and resetting of baroreceptors as the underlying pathophysiological mechanisms. Evidence suggests that regular practice of yogasanas and pranayama appears to cause down-regulation of the HPA axis and the sympathetic nervous system (SNS), increases vagal activity, improves baroreceptor sensitivity, and thereby helps to reduce blood pressure. Although the exact mechanism of beneficial effects of yoga are not known, evidence suggests that yogic intervention may be acting through multiple mechanisms simultaneously influencing diverse neural structures involved in the regulation of the neuroendocrine and the cardiovascular response to stress to cause neurohumoral modulations resulting in alleviation of stress and improvement in cardiovascular indices.

**Keywords:** stress, hypertension, hypothalamic-pituitary-adrenal axis, sympathoadrenal system, baroreceptors, yoga

## 1. Introduction

Fast pace of life, growing aspirations of people, peer pressure and collapsing social support institutions like family, are affecting peoples' health in modern society. Stress and stress-related disorders are emerging as a major health challenge across the globe. Stress is perceived as an event or experience that invoke a range of unpleasant emotions like uneasiness, nervousness, anxiety, and fear. More scientifically speaking stress is a state of disharmony or threatened homeostasis provoked by psychological, environmental, and/or physiological factors called 'stressors'. Stress is often implicated in the pathogenesis of non-communicable diseases like hypertension, coronary heart disease, depression, and obesity. Evidence suggests that dysregulation of stress system is causally linked to the pathogenesis of essential hypertension, with over activity of Hypothalamic-pituitary-adrenal axis (HPA) and Sympathoadrenal System (SAS) and resetting of baroreceptors as the underlying pathophysiological mechanisms.

Non-pharmacological interventions such as relaxation techniques in the form of yoga and meditation are slowly gaining recognition as an adjunctive therapy in case

of stress-related health disorders like hypertension, anxiety, and depression. Yoga promises to be one of the best and relatively safest methods to counter stress. The most popularly used yoga intervention techniques include yogasanas (yoga postures) and pranayama (controlled breathing techniques) and meditation. Asanas and pranayamas reduce stress, relax and revitalise body. Relaxation helps to control anxiety, calms mind and brings down heart rate and blood pressure.

## **2. Concept of stress, allostasis and allostatic load**

All living organisms strive towards a dynamic equilibrium, which is called homeostasis. Homeostasis is maintenance of relative stability of the core parameters required for cell survival [1]. In the classical stress concept, stress can be broadly defined as an actual or anticipated disruption of homeostasis by certain physical and/or psychological events that are known as 'stressors' [2].

Modern concept of stress defines it as a consciously or unconsciously perceived threat to homeostasis [3], which involves specific response of the body that in turn depends on the factors like the nature of the challenge to homeostasis, the perception of the stressor and the ability to cope with it [4]. A new concept called 'allostasis' was introduced to define and explain stress. Accordingly, the term allostasis refers to the process whereby an organism maintains physiological stability by changing parameters of its internal milieu by matching them appropriately to environmental demands [5, 6]. Thus, homeostasis is a process that keeps us alive whilst allostasis is a process that helps us to adapt to the environmental challenges.

Allostatic load (AL) refers to the cumulative effects of chronic and acute stress on the body. It represents the 'wear and tear' the body experiences when repeated allostatic responses are activated during stressful situations [7]. Allostatic overload is the final stage of the progression of allostatic load, whereby the culmination of physiological dysregulations both at the cellular and organ levels leads to disordered, diseased, and deceased endpoints [8].

The concepts of allostasis, allostatic load and overload are to be understood in the context that the physiological systems involved in allostatic responses help us to adapt to challenges imposed by stressors and the dysregulation or overuse of the same systems due to prolonged exposure to stressors can lead to pathological disorders [7]. Thus, allostasis involves health protective adaptive responses to stressors, whereas, allostatic load is the result of the overuse or dysregulation of the systems involved in allostatic responses that leads to pathological disorders, a state referred to as allostatic overload [6].

## **3. Neurobiology of stress response**

The stress response involves multiple organ systems of the body like central nervous system (CNS), autonomic nervous system (ANS), endocrine system, cardiovascular system and immune system [9]. However, individual's response to stressors is conditioned by the genetic, environmental and developmental factors. The collective stress responses are mediated by largely overlapping circuits in the hypothalamus, the limbic cortex, and many neural elements in the brainstem [10]. The brain triggers stress responses that are commensurate with the nature of the stressor. Accordingly, stress regulatory neuro-circuits activated by a particular stressor are crucially dependent on stressor attributes [2].

Depending on their nature, the stressors can be broadly divided into two categories: Physical or Physiological stressors and Psychogenic or Psychological

stressors. Stressors that produce actual disturbances of homeostasis are considered as physical stressors, e.g. haemorrhage or infection. Whereas, stressors that threaten the current state and are predicted or anticipated based on prior experiences are considered as psychogenic stressors, e.g. aversive environmental stimuli [11]. Thus, physical stressors represent 'Systemic stressors' which are of immediate survival value and are mainly processed by brainstem and hypothalamic regions [2, 11]. By contrast, 'Psychogenic stressors' represent 'Processive' stressors. They require sequential stimulus assembly and processing of signals from multiple sensory modalities in the forebrain and can occur in anticipation of or in reaction to stressful events prior to initiation of a stress response. They involve the 'Limbic stress pathways' for processing information [12]. The vast majority of decisions regarding the initiation of stress responses seem to be made at the level of limbic structures, which communicate information to subcortical sites positioned to interface with ongoing homeostatic feedback [13]. It is also believed that limbic forebrain regions may also contribute to processing of physical stressors, influencing the autonomic responses to stress and the activation of the HPA-axis [2].

### **3.1 Brainstem circuitry in stress response**

The autonomic nervous system (ANS) provides the immediate response to stressors mainly mediated via brainstem circuitry. The brainstem region receives neuronal inputs carrying signals of homeostatic disturbances involving cardiovascular system (CVS), respiratory system (RS) and visceral organs [14], which cause reflex stimulation of sympathetic response [15]. Reflex sympathetic activation represents the classic 'fight or flight' response to stress [2].

Besides this, signals from medulla and spinal cord are sent to other autonomic regulative sites in the hindbrain, midbrain and forebrain. The complex interplay between these neural structures and the descending signals from the hypothalamus and limbic cortex ultimately modulate the autonomic response to stressors [15].

Homeostatic imbalance also triggers signals to the brainstem leading to activation of the HPA axis. Ascending brainstem pathways project to the paraventricular nucleus of the hypothalamus (PVN). Catecholaminergic projections to the PVN originate in the nucleus of the solitary tract (NTS) and C1-C3 regions and represent a major HPA excitatory pathway, promoting corticotropin releasing hormone (CRH) and thereby, adrenocorticotrophic hormone (ACTH) release [16]. NTS projections to PVN also release neuropeptide Y, glucagon-like peptide 1, inhibin  $\beta$ , somatostatin and enkephalin, that can regulate HPA activation [17].

Ascending catecholaminergic pathways mainly mediate systemic-stress responses [14]. However, some non-catecholaminergic NTS cell groups (e.g. glucagon-like peptide 1 neurons) are involved in the generation of HPA responses to both psychogenic and systemic stressors [18]. Thus, NTS appears to be a common site for integration of reactive HPA responses. Neurons throughout NTS are activated by a variety of acute and chronic stressors [19]. In addition to sending projections that target subcortical limbic regions critical for regulating behavioural responses to stress, NTS also receives direct input from the amygdala, the bed nucleus of stria terminalis (BST), and the prefrontal cortex [20]. Thus, NTS is a critical hub for integrating interoceptive and viscerosensory input with descending affective and cognitive information from the limbic forebrain.

### **3.2 Hypothalamic nuclei**

Paraventricular nucleus of the hypothalamus (PVN) acts as a principal integrator of stress signals and is directly involved in regulating HPA axis and autonomic



responses to stressors [2]. As mentioned earlier, the PVN receives its major adrenergic inputs from the A2/C2 regions of NTS, which represents a major HPA excitatory pathway promoting CRH release [16]. The PVN neurons project to the autonomic targets in the brainstem and spinal cord such as the intermediolateral cell column, the parabrachial nucleus, the dorsal motor nucleus of the vagus nerve and the NTS [13]. PVN also receives serotonergic innervation from the median raphe nuclei in the midbrain. Serotonin activates the HPA axis and stimulates ACTH release and secretion of glucocorticoids (GCs) [21].

Many of the hypothalamic regions interact with the limbic inputs and are involved in homeostatic integration. Hypothalamic communications with limbic cortex and their combined downward effect on the HPA and ANS activity modulate responses to stressors with respect to ongoing physiological state.

PVN is heavily innervated by inhibitory GABAergic inputs from limbic regions [22]. Most of these limbic–PVN connections are indirect and are made through the bed nucleus of stria terminalis (BST) and peri-PVN regions of the hypothalamus, enabling it to translate limbic information into modulation of the HPA axis or autonomic activation [23]. While PVN projecting GABAergic neurons from posterior BST nuclei inhibit HPA response to stress, CRH neurons from anteroventral BST nuclei to PVN are responsible for excitation of HPA activity [24].

PVN also receives inhibitory GABAergic innervation from the medial preoptic hypothalamus (mPoA), which receives projections from the hippocampus and the medial nucleus of amygdala (MeA) and is an important site for interaction between limbic inputs and physiological regulatory processes [2].

Lateral hypothalamic neurons are positioned to modulate autonomic and/or HPA tone [2, 25]. The Dorsomedial hypothalamus (DMH) regulates autonomic and perhaps also HPA axis responses to psychogenic stimuli [2]. Suprachiasmatic nucleus (SCN) has effect on the diurnal variations and basal HPA activity and autonomic responses to psychogenic stressors [26]. SCN innervates peri PVN regions, where it interacts with the signals from limbic cortex.

### **3.3 Limbic stress circuits**

The interface between the incoming sensory information about the stressors and the appraisal process is formed by limbic brain structures. Both psychogenic and physical stimuli are processed in multiple limbic forebrain structures, including the amygdala, the hippocampus and the prefrontal cortex [2]. These regions receive associational information from subcortical and cortical areas involved in higher-order sensory processing and memory and also ascending inputs from sites involved in attention and arousal. Limbic structures do not communicate directly with the primary stress effector systems. Instead, they send signals to the subcortical relay sites, which in turn interface with the primary stress effector neurons in the PVN, caudal medulla and spinal cord [14]. Usually, there is interaction between the outputs from the stress-excitatory structures (central (CeA) and medial (MeA) nuclei of amygdala and infralimbic cortex) and stress-inhibitory regions (hippocampus, prelimbic cortex), so that local integration of limbic information occurs before relaying it to the primary stress effector sites [14]. Downward signals from these limbic regions modulate the activity of the HPA axis and probably also autonomic responses to stress [2].

#### **3.3.1 Amygdala**

Studies suggest that the Central nucleus of amygdala (CeA) and the BST coordinate to orchestrate both acute and chronic responses to various kinds of

threatening stimuli and are involved in the control of fear and anxiety [27]. CeA is primarily involved in behavioural, autonomic and endocrine responses to stress [10]. The medial nucleus of amygdala (MeA) and basolateral nucleus of amygdala (BLA) are preferentially activated by psychological stressors [11, 25]. There is a two-way neural communication between amygdala and the dorsal raphe nucleus and catecholaminergic nuclei in the brainstem. CeA sends inputs to CRH neurons in the PVN both directly and through the bed nucleus of the stria terminalis and mediates the adrenocortical response to somatosensory stimuli [2, 10].

### 3.3.2 Hippocampus

The hippocampus inhibits the HPA axis activity. It also influences autonomic tone. Hippocampus has no major direct projections to the brainstem, but its action on autonomic function might be routed through NTS-projecting regions of the medial prefrontal cortex (mPFC) [2].

### 3.3.3 Prefrontal cortex (PFC)

Prefrontal cortex (PFC) is critical to develop appropriate responses to environment changes, enabling behavioural plasticity [28]. The prelimbic medial PFC (mPFC) preferentially inhibits HPA axis response to psychogenic stressors and, like the hippocampus it is involved in response termination [2]. The infralimbic PFC is involved in initiating autonomic and HPA responses to psychogenic stimuli. The infralimbic cortex is selectively involved in stress induced cardiovascular regulation, perhaps through modification of the baroreflex activity. As a result of its interconnections with the hippocampus and the amygdala, the prefrontal cortex is positioned at the top of the response initiation hierarchy and might be a principal limbic coordinator of physiological reactivity [2].

## 3.4 Circumventricular organs (CVO)

PVN projections from subfornical organ (SFO) are angiotensinergic and also promotes CRH secretion and biosynthesis [29]. This pathway may be involved in fluid/electrolyte balance stress induced stimulation of HPA-axis activity via activation of the angiotensin II type-1 receptor [30]. There are projections from organum vasculosum of the lamina terminalis (OVLT) to the anteroventral preoptic nucleus, DMH and preautonomic PVN. These pathways are believed to be responsible for initiating cardiovascular response to stress [31].

## 4. Primary mediators of stress response

The body's responses to stressors are mediated by an intricate stress system, which includes the hypothalamic–pituitary–adrenal (HPA) axis and the sympatho-adrenal system (SAS), which consists of sympathetic nervous system (SNS) and adrenomedullary system (AS) [32]. The hormones of HPA axis and catecholamines released by SAS are the primary mediators of the stress response [33].

As mentioned earlier the paraventricular nucleus of hypothalamus (PVN) plays a major role in stress response. Stress induced activation of the parvocellular neurons of the PVN causes the release of CRH and Arginine vasopressin (AVP) and initiates the endocrine response to stressors. CRH controls ACTH release from the anterior pituitary gland [10]. AVP is co-localised with CRH in

parvocellular neurons of PVN. In the anterior pituitary, AVP potentiates the effect of CRH on ACTH release [34]. Reciprocal connections exist between CRH neurons in PVN and noradrenergic neurons in the locus ceruleus (LC); hence, they stimulate each other in a positive feedback fashion [33]. CRH serves as a neurotransmitter that mediates sympathetic arousal, providing a link between the adrenocortical and autonomic branches of the stress response. The locus ceruleus-norepinephrine system (LNE) controls the stress-induced stimulation of the sympathoadrenal system (SAS) [10]. ACTH is the key regulator of glucocorticoid secretion from the adrenal cortex. Glucocorticoid hormones, mainly cortisol in humans, and cortisone in animals, are the final effectors of the hypothalamic-pituitary-adrenal axis (HPA) axis, which mediate the response of the organism to stressors [10].

## **5. Acute vs. chronic stress response: protection vs. damage**

The first phase of the acute stress response involves activation of sympathoadrenal system (SAS), which results in a typical 'fight-or-flight' responses. These are rapid but short-term physiological adaptations, so as to meet the challenge imposed by a stressful event. It is mediated by the release of catecholamines like norepinephrine (NE). Whereas, the secondary phase involves the hormonal mechanism (hypothalamic-pituitary-adrenal axis) considered sluggish compared to the synaptic mechanisms that activate the SAS, but resulting in an amplified and protracted secretory response involving stress hormones like CRH, ACTH and glucocorticoids (GCs), mainly cortisol in human beings (long-lasting response). Cortisol in turn has effects all over the body including brain [13].

In acute stress response, the action of SAS and HPA axis mediators is protective in nature and is geared to enable the individual to adapt to stressors. However, chronic exposure to stressors results in over-activation and or dysregulation of SAS and HPA-axis to induce a chain reaction of deleterious effects on the biological systems involved in stress response, which eventually leads to stress-related disorders [35]. Stress induced brain changes further diminish the body's ability to cognitively process and physiologically respond to stressors [36]. In chronic stress, prolonged and synergistic effects of the stress hormones and pro-inflammatory cytokines adversely affect multiple interconnected organ systems (autonomic, neuroendocrine, immune and cardiovascular systems) involved in stress response, which finally results in various pathological conditions [8].

## **6. Aetiology of essential hypertension**

Essential hypertension is a multifactorial disorder with a strong genetic predisposition. Multiple studies have suggested involvement of many factors in the genesis of essential hypertension. The principal factors among them are: increased activity of SNS including renal SNS; over activity of renin-angiotensin-aldosterone system (RAAS); positive sodium imbalance; low levels of vasodilators, like nitric oxide (NO), prostacyclin (PGI<sub>2</sub>), and the natriuretic peptides; high levels of vasoconstrictors like endothelin 1 (ET 1); structural and functional vascular defects; increased activity of vascular growth factors; and obesity [37]. In recent studies, oxidative stress, endothelial dysfunction, vascular remodelling and decreased vascular compliance are implicated as the primary antecedents, which may be involved in the development of essential hypertension [38].

## **7. Role of stress in pathogenesis of essential hypertension**

Due to the complexity of the mechanisms controlling blood pressure regulation and involvement of many interconnected regulatory organ systems, with various endogenous and exogenous factors interacting with these regulatory systems, the exact cause of essential hypertension is still not known [39].

Although stress is clearly implicated in the aetiology of essential hypertension, the relationship between a psycho-physiological construct like stress and the physical manifestation of essential hypertension is not simple or direct. It is quite likely that multiple etiologic pathways as well as the variety of intervening variables exist that lead to the onset of essential hypertension. However, psychological stress has been considered to be one of the major risk factors for essential hypertension [40–42].

### **7.1 Cardiovascular reactivity and essential hypertension**

There have been many studies which suggest that, the exaggerated cardiovascular response (CVR) to life stressors appear to play a key role in the stress–hypertension relation [43, 44]. It has been suggested that, heightened cardiovascular reactivity could reflect sympathetic hyper responsivity or enhanced vagal withdrawal during stress, whereas poorer cardiovascular recovery could be due to prolonged sympathetic activation, diminished vagal tone, or attenuated or delayed vagal rebound following the termination of stress [45]. It is believed that increased cardiovascular reactivity and poor cardiovascular recovery could indicate autonomic dysregulation of cardiovascular system, which may be contributing in the pathogenesis of essential hypertension [46].

### **7.2 Chronic stress and essential hypertension**

Evidence suggests that chronic exposure to psychosocial stress leads to the onset of essential hypertension via stress response, which includes the affective, cognitive, behavioural, and physiological alterations. Stress induced increased sympathetic activity, decreased vagal activity, reduced baroreflex gain, over activity of the hypothalamic-pituitary-adrenal (HPA) axis and endothelial dysfunction as a long-term consequence, cause increase in blood pressure and heart rate by affecting central and peripheral regulation of the CVS [47].

There is a mount of evidence linking chronic stress with essential hypertension. Clinical and epidemiological studies indicate that chronic psychological stress can lead to essential hypertension [48, 49]. Many workers in their studies have found that individuals exposed to chronic stress show persistent hypertension [40, 50, 51]. Various population studies have demonstrated that psychosocial stress is associated with an increased risk of hypertension [52, 53]. Studies have also found that stress induced alterations in blood pressure persist even after the end of exposure to stressors [54, 55].

### **7.3 Possible mechanisms leading to essential hypertension**

#### *7.3.1 Increased activity of sympathetic nervous system*

Chronic exposure to stressors leads to dysregulation of autonomic nervous system and increase in the activity of HPA axis. Dysregulation of ANS causes increase in the activity of sympathetic nervous system (SNS), which further



augments the activity of HPA axis [56]. Activation of SNS leads to enhanced release of NE, Nitric oxide (NO) and Neuropeptide Y (NPY) from sympathetic nerve terminals [57].

Stimulation of sympathetic nervous system is a pathophysiological hallmark of essential hypertension, and especially, hypertension attributable to chronic mental stress [40, 58, 59]. Increased SNS activity leads to the development of hypertension by several mechanisms like peripheral vasoconstriction, increased cardiac contraction, renal sodium and water retention, baroreflex dysfunction, and vascular damage [60, 61]. Chronic sympathetic stimulation causes left ventricular hypertrophy and dysfunction, and arterial remodelling [62]. Repeated stress-induced vasoconstriction may also result in vascular hypertrophy, leading to progressive increases in peripheral resistance and blood pressure [63].

NE and NPY modulate the release of pro-inflammatory cytokines, such as Interleukin-6 (IL-6), C-reactive protein (CRP), and tumour necrosis factor (TNF) [52]. These cytokines in turn cause inflammation and endothelial dysfunction and lead to development of hypertension [64].

The mechanisms underlying dysregulation of sympathetic nervous system activity involve impairment in sympathetic restraint due to alterations in arterial and cardio-pulmonary baroreflexes and central/peripheral chemoreflexes or error in the processing of reflex signals in brainstem cardio vascular centre [65]. Resetting of the baroreflex to a higher pressure and reduced baroreflex sensitivity are important mechanisms underlying essential hypertension [66, 67]. Resetting of baroreflex can be at afferent, central or efferent level [68]. Afferent component can be altered by defective mechanosensitive transduction in case of decreased vascular compliance and loss of coupling of vessel wall stretch to baroreceptors [67]. Prolonged stimulation of CNS via baroreceptor afferents may result in remodelling of the neural networks involved in the processing of baroreceptor signals. CNS 'rewiring' may be contributing to the resetting, adaptation, and post excitatory depression of the baroreceptors. This resetting in CNS could be due to decreased responsiveness of the medullary autonomic regulatory centres to baroreceptor signalling. Central resetting of baroreceptors causes sympathetic activity to 'escape' the inhibitory effect of baroreflex [69]. Evidence also shows that angiotensin II, aldosterone and reactive oxygen species (ROS) may be involved in the centrally mediated changes in baroreflex efferent activity, which contribute to sympathetic over activity in hypertension [69].

Sympathetic outflow also affects renal regulation of blood pressure. Stimulation of the renal sympathetic outflow is thought to be a common final pathway in the pathogenesis of essential hypertension in chronic stress [51, 52]. The activation of renal sympathetic nerves underlines the concurrent 'neural', 'renal', and 'sodium' mechanisms leading to the development of hypertension. Stimulation of renal sympathetic nerves is believed to have direct and indirect effects (through RAAS) on renal 'pressure-natriuresis' mechanism inducing sodium and water retention, causing volume expansion and increased blood pressure [70].

### *7.3.2 Over activity of HPA axis*

Dysregulation of HPA activity due to stress especially psychogenic stress, causes marked enhancement in basal HPA tone causing enhanced CRH and AVP synthesis [71], increase in the baseline glucocorticoid secretion, adrenal hypertrophy [72], down regulation of glucocorticoid receptors (GR) in feedback regions, such as hippocampus and prefrontal cortex [71], enhancement of cortisol response to stressors [73], blunting of glucocorticoid negative feedback effect [74], and increased anxiety and depression [75].

Activation of HPA axis involves increased secretion of CRH and AVP in the hypothalamus. AVP in turn potentiates CRH activity [76]. CRH stimulates production of ACTH by the anterior pituitary gland. ACTH then acts on the adrenal glands to cause release of glucocorticoids (GCs), mainly cortisol and mineralocorticoids (MRs). In addition to being a principal regulator of the HPA axis, CRH also causes stimulation of SNS activity [77]. Glucocorticoids stimulate biosynthesis, secretion and release of catecholamines (CA) by sympathetic nerves and adrenal medullary cells [78], and enhance vasoconstrictor effects of angiotensin-II and catecholamines and it has also been implicated in endothelial dysfunction [79]. Thus, synergistic and prolonged actions of CRH, glucocorticoids and catecholamines cause central and autonomic dysregulation of cardiovascular system, which eventually leads to hypertension.

### *7.3.3 Renin-angiotensin-aldosterone system (RAAS)*

Renin-angiotensin-aldosterone system (RAAS) plays an important role in the development of stress induced hypertension [80, 81]. Angiotensin II is the main effector of RAAS, which increases blood pressure by various mechanisms including, increase in the sympathetic outflow from the brain, constriction of resistance vessels, stimulation of aldosterone secretion, increase in renal tubular sodium reabsorption directly and indirectly, stimulation of thirst, and release of AVP hormone [38]. Angiotensin II modulates 'pressure natriuresis' mechanism in the kidneys and contribute to the development of RAAS-dependent blood pressure dysregulation in hypertension [82].

Evidence suggests that activation of angiotensinergic pathways in the central nervous system (CNS) plays a critical role in the development of hypertension by circulating angiotensin II or aldosterone [10]. Most of the actions of angiotensin II are mediated by angiotensin II type 1 receptors (AT1), which are expressed in a number of brain regions like, circumventricular organs (CVOs), hypothalamus, brainstem and parts of limbic cortex associated with the emotional stress response like, the amygdala, bed nucleus of stria terminalis (BST) and other limbic regions [83]. Projections from limbic regions extend to the areas involved in autonomic control of blood pressure, namely, circumventricular organs (CVOs) including Subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT) [84]. Angiotensinergic sympatho-excitatory neurons in CVO project to the paraventricular nucleus (PVN), and the PVN neurons in turn project to the rostral ventrolateral medulla (RVLM) in the brainstem or directly to the intermediolateral cell column in the spinal cord [85]. Circulating angiotensin II or angiotensin II released from nerve terminals bind to AT1 receptors and cause activation of presympathetic neurons thereby increasing SNS activity and blood pressure [86]. Thus, circulating angiotensin II acts as a major signal to the CNS that contributes to the development of hypertension. Angiotensin II not only exerts the central effects mentioned above to increase sympathetic outflow, but also has direct effects on postganglionic fibres to enhance the release of catecholamines [87].

Angiotensin II also promotes vasoconstriction [88], and is a potent stimulus for pro-inflammatory and pro-oxidative events leading to endothelial dysfunction, vascular remodelling and eventual development of hypertension [89, 90]. Angiotensin II exerts vascular damage by generation of reactive oxygen species (ROS) and stimulation of redox-dependent signalling pathways [91].

### *7.3.4 Immune dysfunction and inflammation*

Psychological stress can affect immune function by activating sympathoadrenal system (SAS) as well as the HPA axis to release catecholamines (adrenaline and

noradrenaline), ACTH, and glucocorticoids (cortisol). These stress hormones in turn induce immune modulation leading to production of pro-inflammatory cytokines, including C-reactive protein (CRP), tumour-necrosis factor (TNF $\alpha$ ), Interleukin-6 (IL-6), Interleukin-1 (IL-1 $\beta$ ), Interleukin-2 (IL-2), and the transcription factor of nuclear factor kappa B (NF- $\kappa$ B) [92]. Immune modulation can also occur directly through the binding of the stress hormones to their receptors on the surface of the immune cells as almost all immune cells express receptors for one or more of the stress hormones [93].

Various studies suggest that hypertension is a state of chronic low grade inflammation, that is characterised by the infiltration of immune cells into the interstitium of affected organs, (mainly kidneys, blood vessels, brain and heart), where they release pro-inflammatory cytokines and promote oxidative stress, which then leads to dysfunction of these organs, causing hypertension and eventual end-organ damage [94, 95]. Thus, inflammation in the kidneys, vessels, and CNS plays a major role in the pathogenesis of hypertension [96].

Evidence shows that hypertensive patients have increased levels of circulating monocytes, lymphocytes and pro-inflammatory cytokines, such as tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin (IL) 6 and C-reactive protein [97]. Vascular inflammation is characterised by an accumulation of macrophages, monocytes, dendritic cells, B and T lymphocytes; moreover, increased expression of pro-inflammatory cytokines and cell adhesion molecules in different layers of the vascular wall induce extracellular matrix deposition, smooth muscle hypertrophy, and endothelial dysfunction, contributing to the development and maintenance of arterial hypertension [98]. Immune cells and cytokines stimulate formation of reactive oxygen species (ROS) by vascular smooth muscle cells and endothelial cells, which in turn causes endothelial dysfunction and hypertension [95].

Several studies show that hypertension is associated with accumulation T cells, monocyte/macrophages and dendritic cells in the kidneys. Cytokines secreted by innate and adaptive immune cells, as well as renal epithelial cells, modulate the expression and activity of sodium transporters along the nephron, leading to defective pressure natriuresis, sodium and water retention, and hypertension [95, 99]. Cytokines produced by T cells, especially IL -17 A, play an important role in pathogenesis of hypertension due to renal inflammation. Renal inflammation, immune cell infiltration, and augmented angiotensin II activity blunt pressure dependent natriuresis and cause hypertension [100].

The central nervous system (CNS), the sympathetic nervous system (SNS), and the immune system are interconnected in the physiological modulation of hemodynamic and immune activity [101]. Inflammatory cells and cytokines can impair central autonomic control of blood pressure regulation [102]. CNS can serve as both a target for inflammatory cells in hypertension and as a mediator of inflammation through its communication with the immune system. Angiotensin II is a key contributor to these processes in the setting of hypertension. Angiotensin II causes T cell activation and vascular inflammation especially in CVO region of the brain and leads to hypertension [103].

### *7.3.5 Oxidative stress and endothelial dysfunction*

There is increasing evidence that oxidative stress is strongly associated with essential hypertension [104]. Many studies have shown that chronic psychological stress promotes oxidative stress throughout the body [105, 106]. Oxidative stress occurs when there is over production of oxidant agents, reactive oxygen species (ROS) that overwhelm the cellular antioxidant defence system. Oxidative



stress causes endothelial dysfunction and thus contributes to the development of hypertension [107].

Endothelial dysfunction involves alteration of the endovascular lining of blood vessels that is characterised by a pro-thrombotic, pro-inflammatory, and pro-constrictive phenotype [107]. An imbalance in the homeostasis of the endothelial derived relaxing factors like NO and prostacyclin (PGI<sub>2</sub>) and endothelial derived constricting factors like endothelin 1 (ET 1) and angiotensin II, is a major feature in endothelial dysfunction, that leads to functional changes in the microvasculature with a predominant and deleterious constrictive tone, which causes increased peripheral resistance and hypertension [108].

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have an important role in the homeostasis of the vascular wall, hence they are implicated in the pathogenesis of hypertension [109]. The most important ROS within the vasculature include the superoxide anion, hydrogen peroxide, hydroxyl radical and RNS being peroxynitrite. Physiologically, ROS generation is tightly regulated by endogenous cellular antioxidants, which include superoxide dismutase (SOD), catalase, thioredoxin, glutathione, and antioxidant vitamins [110]. In hypertension, there is a mismatch between ROS production and protective antioxidant mechanisms in the cells, leading to a state of oxidative stress [111].

Oxidative stress may contribute to the development and/or maintenance of hypertension via numerous mechanisms. ROS such as superoxide combines with nitric oxide (NO), to form peroxynitrite. This reduces bioavailability of NO causing impaired endothelial derived vasodilation [112]. Free radical induced generation of lipid peroxidation products, such as F<sub>2</sub>-isoprostanes have vasoconstrictor effect and thus can modulate the vascular tone [113]. Superoxide leads to oxidation of tetrahydrobiopterin (BH<sub>4</sub>), which promotes endothelial nitric oxide synthase (eNOS) uncoupling and causes further production of ROS [114]. ROS also adversely affects blood vessels leading to structural remodelling and vascular dysfunction [115]. When produced in excess, ROS has many deleterious effects that results in endothelial dysfunction, increased vascular contractility, vascular remodelling, vascular inflammation, growth of vascular smooth muscle cells and apoptosis, lipid peroxidation and deposition of extracellular matrix proteins, all the major processes involved in pathogenesis of hypertension [116, 117].

Evidence also suggests an interrelationship between immune response and oxidative stress. Oxidative stress induced immune activation mechanism have been proposed in the pathogenesis of hypertension [95, 118]. It has been proposed that oxidative stress-induced ROS causes production of 'isoketals' by fatty acid oxidation, which serve as autoantigens [119]. Autoantigens then cause T cell proliferation and increased production of pro-inflammatory cytokines such as chemokine (C-C motif) ligand 2 (CCL2), IL-1, IL-6, IL-17A, and TNF- $\alpha$  in the kidneys, blood vessels and other tissues [89, 120]. These inflammatory mediators along with catecholamines and other blood pressure elevating hormones mutually exert their actions to cause vascular and renal dysfunction, which ultimately results in development of hypertension [119].

#### **7.4 Mediators of inflammation and endothelial dysfunction: a possible causative link between stress and pathogenesis of essential hypertension**

Chronic inflammation and endothelial dysfunction play a crucial role in the development and progression of essential hypertension [121–123]. Prolonged exposure to stress generates, on the one hand, a state of chronic inflammation, which adversely affects the health and integrity of the endothelium [124]; and, on the



other hand, activation of the HPA axis and the SNS, which produce mediators that directly affect the organ systems involved in blood pressure regulation [125]. Some of the mediators which may be central to the inflammatory mechanisms contributing to the pathogenesis of hypertension are listed below.

#### *7.4.1 Immune cells*

As mentioned earlier infiltration of immune cells into the interstitium of kidneys, brain, heart, and blood vessels and release of cytokines cause inflammation and leads to the development of hypertension. It has been found that the number of circulating 'immunosenescent' pro-inflammatory CD8<sup>+</sup> T cells is increased in hypertensive patients. These cells produce pro-inflammatory cytokines like IFN- $\gamma$  and TNF- $\alpha$ , and the cytotoxic molecules, granzyme B and perforin [126]. These cells also express mineralocorticoid receptors, which play a major role in development of systemic hypertension by promoting production of IFN- $\gamma$  [127]. It has been shown that IL-17A, produced by CD4<sup>+</sup> T cells and  $\gamma/\delta$  T cells, plays a critical role in hypertension [128, 129]. Clinical and experimental hypertension is associated with raised serum IgG, IgA or IgM antibodies produced by B cells [130]. Autoantibodies that are agonistic to angiotensin type 1 receptor (AT1 R) are found to be present in hypertensive patients [131, 132]. Monocytes and macrophages have been implicated in various models of experimental hypertension [133, 134]. They accumulate in the perivascular tissue, adventitia and kidneys [135] and promote the release of pro-inflammatory mediators and free radicals via NADPH oxidase 2 (NOX 2) to cause inflammation [136]. Studies indicate that Dendritic cells (DCs) play a role in the development of hypertension. DCs in hypertensive animals produce an increased amount of superoxide and cytokines (IL-1 $\beta$ , IL-6, IL-23), which affects T cell polarisation into the inflammatory phenotype [137].

#### *7.4.2 Cytokines*

Cytokines produced by immune cells have deleterious inflammatory effects on the kidneys, blood vessels, heart and brain. IL-17A contributes to angiotensin II (Ang II)-induced renal injury and modulates the expression of renal sodium transporters affecting pressure natriuresis [138, 139]. Interferon Gamma (IFN- $\gamma$ ) produced by TH1 cells, CD8<sup>+</sup> T cells (TC1 cells) and natural killer T cells, affect local renin-angiotensin system and along with IL-17A, it is found to alter the expression of renal sodium transporters in proximal and distal tubules to directly affect pressure-natriuresis mechanism [139]. Tumour Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), produced by T cells, macrophages, and endothelial cells, decrease the renal tubular expression of eNOS affecting NO production, which leads to sodium retention [140, 141]. Interleukin 6 (IL 6) produced by dendritic cells, macrophages, monocytes, and TH1 cells is considered to be a major signal to promote polarisation of CD4<sup>+</sup> T cells to produce IL-17A [138]. IL-17A is implicated in the angiotensin induced hypertension [142].

Studies also show that IL-17A causes vascular dysfunction by increasing superoxide production and reduced NO production by impairing eNOS activity [94, 128, 138]. TNF- $\alpha$  affects endothelial eNOS expression, affecting production of NO by endothelial cells [143]. TNF- $\alpha$  also activates NF- $\kappa$ B and NADPH oxidase [143], which causes induction of oxidative stress and overexpression of both chemokines and adhesion molecules [144]. IFN- $\gamma$  causes superoxide production via upregulation of the expression and activity of NADPH oxidases in human aortic smooth muscle cells [145]. It acts directly on vascular smooth muscle cells to induce their proliferation and apoptosis [146]. IL-6 mediates elevation of superoxide production and

endothelial impairment by affecting NO-cGMP pathway [147]. IL-6 has also been reported to play a role in vascular smooth muscle cells migration and proliferation causing vascular medial hypertrophy [148].

#### *7.4.3 Corticotropin-releasing hormone (CRH)*

Besides being produced in nervous system, CRH is also an autocrine and paracrine mediator in tissues like endothelium. In vitro studies show that CRH dose-dependently induces the release of endothelin-1 (ET-1) [149], causes increase in reactive oxygen species (ROS) content, increased catalase activity, and peroxynitrite levels as well as a decrease in the activity of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) production [150]. It also cause increased vascular permeability, and cytokine release further affecting vascular health [151].

#### *7.4.4 Glucocorticoids (GCs)*

Circulating high level of GCs in hypertensive patients are believed to cause over-production of ROS and reduced availability NO in the vascular endothelium. The GC-induced decrease in NO availability may elicit vascular endothelial dysfunction, leading to hypertension. GCs are also believed to stimulate release of vasoconstrictor endothelin 1 (ET 1) and increase vascular tone [56].

#### *7.4.5 Endothelin 1 (ET 1)*

ET-1 are powerful vasoconstrictor peptides produced by variety of tissues including vascular endothelium, heart, and kidney epithelial cells. The synthesis of ET-1 is stimulated by angiotensin II, AVP, norepinephrine, glucocorticoids, hypoxia, shear stress, lipoproteins, oxidative stress [152] and of particular interest, by acute mental or physical stress [153]. Studies have shown that ET-1 at the central level plays an essential role in the cardiovascular sympathetic response to stress [154]. Besides its vasoconstrictive action, ET-1 causes fibrosis of the vascular wall, mitotic stimulation of vascular smooth muscle, increased production of ROS (superoxide) and is pro-inflammatory [155]. ET 1 contributes to the development of inflammatory mechanisms by activating transcription factor- $\kappa$ B, and by increasing production of pro-inflammatory cytokines like,  $\text{TNF}\alpha$ , IL-1, and IL-6. ET 1 also induces cyclooxygenase-2 (COX-2) expression and prostaglandin E2 (PGE 2) release by mitogen-activated protein kinase (MAPKs) and NF- $\kappa$ B. Cyclooxygenase-2 is involved in the development of vascular inflammation [156].

#### *7.4.6 Angiotensin II and aldosterone*

Angiotensin II induces an inflammatory response in the kidneys, heart and vasculature by increasing the expression of pro-inflammatory chemokines, and also causes T cell mediated inflammation [157]. Angiotensin II is one of the major vasoactive peptides involved in the regulation and activation of NAD(P)H oxidase, a major source of ROS in the vascular wall, and thus, it contributes to the production of ROS in vascular smooth muscle cells and endothelial cells [110]. Through ROS generation, angiotensin II exerts several deleterious vascular effects, including functional and structural changes, which results in hypertension [158]. Angiotensin II also promotes endothelial dysfunction through cyclooxygenase-2 (COX-2) activation, which generates vasoactive thromboxane A2 and ROS [159].

Aldosterone has been reported to exert mineralocorticoid receptor mediated pro-inflammatory effects in vessels, heart and kidneys [64]. It induces

inflammation by stimulating the formation of reactive oxygen species such as superoxide and hydrogen peroxide [160]. In the heart, aldosterone can increase vascular expression of intracellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), osteopontin, and COX-2, to cause inflammation [161]. In the kidneys, aldosterone has been shown to cause inflammation by leukocyte infiltration and elevation of osteopontin, IL-6, IL-1 $\beta$ , and MCP-1 levels [162].

#### *7.4.7 Reactive oxygen species (ROS) and reactive nitrogen species (RNS)*

ROS/RNS are strongly implicated in the pathogenesis of hypertension by causing oxidative stress, endothelial dysfunction and inflammation. ROS are derived from oxygen reduction which produces, through several steps, important intermediate products: superoxide anion, hydrogen peroxide, and hydroxyl radical [104]. Some of the enzymes involved in ROS generation are: nitric oxide synthase, peroxidases, NADPH oxidase, NADPH oxidase isoforms (NOX), xanthine oxidase (XO), lipoxygenases (LOXs), glucose oxidase, and cyclooxygenases (COXs) [163]. RNS derives from nitric oxide (NO) that is generated by the NADPH-dependent enzyme nitric oxide synthase [164]. NO is a free radical but is relatively stable. NO is able to form other nitrogen reactive intermediates (nitrate, peroxynitrite, and 3-nitrotyrosine), which affect cell functions [165].

ROS are potent modulators of vascular contraction, dilatation, and structural remodelling by processes such as reducing bioavailability of NO by superoxide anion ( $O_2^-$ ), generation of vasoconstrictor lipid peroxidation products (F<sub>2</sub>-isoprostanes), depletion of tetrahydrobiopterin (a key cofactor for NO synthase), activation of pro-inflammatory transcription factors, stimulation of growth factor production, and induction of fibrosis through activation of matrix metalloproteinase [166]. These processes induce increased intracellular calcium, activation of growth and inflammatory signalling pathways, and increased extracellular matrix deposition, leading to endothelial dysfunction, increased vascular smooth muscle reactivity, and vascular remodelling [167]. All of these factors contribute to the development of hypertension.

## **8. How does stress cause hypertension?**

The answer to this question is not simple or straight forward. However, it is evident from the above discourse that stress, especially chronic psychological stress directly affects neuro-endocrinal control of blood pressure regulatory systems and contribute to the development and progression of essential hypertension. Central to the pathogenesis of hypertension is the over activity of SNS and HPA axis. Increased sympathetic outflow and HPA system hyperactivity act synergistically to potentiate the actions of each other and results in a cascade of deleterious effects on the various inter-connected organ systems involved in blood pressure regulation. Principle among these organs are kidneys, brain, heart and blood vessels, which may suffer eventual structural and functional deterioration. The consequences of these effects are baroreflex dysfunction, stimulation of RAAS activity, activation of immune cells, oxidative stress and endothelial dysfunction. The end result of these effector mechanisms is manifested in several different ways affecting the target organs; in kidneys, altered pressure dependent natriuresis leading to sodium retention and fluid volume expansion, in blood vessels, vascular inflammation, increased vascular contractility, vascular remodelling and arterial stiffness all causing increased peripheral resistance, and in heart, cardiac injury, fibrosis of heart

and cardiac hypertrophy. Combination of all these factors eventually lead to the development of essential hypertension.

## **9. Yoga as a therapeutic intervention for the management of essential hypertension**

Yoga is an ancient Indian discipline designed to bring balance and health to the physical, mental, emotional, and spiritual dimensions of the individual [168]. Numerous studies have shown yoga to have beneficial effects on cardio-vascular indices in hypertensive patients. The exact underlying mechanisms of the beneficial effects of yoga in hypertension still remain elusive. However, there is a reason to believe that yoga may be having multiple and simultaneous effects on diverse neuro-endocrine regulatory structures to cause neurohumoral modulation resulting in alleviation of stress and improvement in cardiovascular behaviour. Thus, yoga seems to have beneficial effects in essential hypertension by two-way action of simultaneously influencing blood pressure regulatory mechanisms as well as stress regulatory mechanisms.

Various neurophysiological mechanisms have been proposed in previous studies to explain the beneficial effects of yoga therapy in hypertension. Following sections describe some of the possible neuro-endocrine mechanisms underlying the beneficial effects of yoga in essential hypertension.

### **9.1 Down-regulation of HPA axis and SNS activity**

There is increasing evidence that yoga appears to have widespread beneficial effects on the cardiovascular response to stress in healthy and hypertensive individuals through down-regulation of the HPA axis and the sympathetic nervous system (SNS) [168, 169].

In various studies, it has been found that regular practitioners of yoga asanas showed a significant reduction in the blood levels of adrenaline, noradrenaline and plasma rennin activity [170, 171]. The attendant reduction in catecholamines and cortisol, decline in cardiovascular reactivity, enhancement of mood and well-being, and alleviation of perceived stress may result in positive downstream effects on metabolic and hemodynamic profiles [168, 171, 172]. Yoga thus significantly decreases heart rate and systolic and diastolic blood pressure probably by its quietening effect on HPA axis and SNS activity [168, 171, 173].

Down regulation of HPA axis and SAS by yoga may be brought by the actions of yoga on different neural structures involved in stress response and cardiovascular regulation. It has been proposed that yoga may be acting at the level of the paraventricular nuclei (PVN) of the hypothalamus, which is a principal integrator of stress signals involved in regulating HPA axis and autonomic responses to stressors. Evidence suggests that the yogic practices probably inhibit the activity of PVN with the resultant decrease in ACTH release from anterior pituitary which in turn decreases the synthesis of cortisol from the adrenal glands [174]. Cortisol also tends to activate phenyl ethanolamine-*N*-methyl transferase (PNMT) required for conversion of norepinephrine to epinephrine. Consequent to sympathetic inhibition and a decrease in PNMT, catecholamine formation decreases. The decreased levels of corticosteroids and catecholamines are known to decrease stress responses [174, 175].

Yoga may also be causing inhibition of the posterior hypothalamus to decrease sympathetic activity and thus, may restore autonomic balance between sympathetic and parasympathetic limbs to alleviate stress [174–176].



Yoga may also be acting at the level of limbic cortex and/or higher cortical centres to modulate autonomic response to stress. It has been proposed that regular practice of yoga results in modulation of autonomic response such that there is a predominant parasympathetic effect and reduced sympathetic tone, which causes reduction in heart rate and blood pressure. Furthermore, it is suggested that this modulation of autonomic balance may be mediated through the limbic system and higher cortical areas resulting in the inhibition of posterior nuclei of hypothalamus leading to decreased discharge through descending autonomic fibres [176–178].

Studies have also shown that regular practice of yoga is associated with the reduction in the basal cortisol and catecholamine secretion, decrease in sympathetic activity with the corresponding increase in parasympathetic activity [179]. It is believed to be due to the alleviation of stress by yoga. Stress relieving effect of yoga may be due to modulation of limbic signals, which may alter sympathetic activity and hormonal response during stress via hypothalamus [180, 181]. Yoga might also be involved in upregulation of hippocampal 5HT<sub>1A</sub> receptors leading to decrease in cortisol levels and thus helping to relieve stress [179].

In a study, which assessed the effect of yoga based guided relaxation on autonomic variables, it was found that there was a decrease in heart rate and skin conductance levels along with the decrease in power of the low frequency component of heart-rate variability and increase in the power of high frequency component, which could be attributed to decreased sympathetic tone after guided relaxation [182]. In other studies involving yoga intervention in depressed patients, significant reductions in low-frequency heart rate variability (HRV); a sign of sympathetic nervous system activation, was noted following yoga intervention [168, 183].

Regular practice of slow pranayamic breathing is also known to reduce sympathetic nerve traffic and increase parasympathetic activity [184, 185]. One of the long-term effects of pranayamic breathing is the improvement in autonomic function. Specifically, with slow breathing pranayama there is a noted increase in parasympathetic activity and a decrease in sympathetic dominance [177, 184]. Short-term effects of slow pranayamic breathing include increased galvanic skin resistance, decreased heart rate, decreased blood pressure and increased amplitude of theta waves indicating increased parasympathetic activity. Both the short term and long-term effects of pranayamic breathing indicate a dynamic alteration of the autonomic system tilting the balance in favour of parasympathetic dominance [184, 186]. It is proposed that slow deep pranayamic breathing shifts the autonomic balance to parasympathetic dominance by two mechanisms: (1) Inflation of lungs above tidal volume during pranayama stimulates stretch receptors in the lungs. Stimulation of stretch receptors increases the frequency and duration of inhibitory neural signals that are known to elicit synchronisation of neural activity in the cardio-respiratory centre in the brainstem [187] and CNS especially hypothalamus [188]. Synchronisation within the hypothalamus and the brainstem [189] may be responsible for inducing the parasympathetic response [190] during breathing exercises. (2) Pranayama also causes stretching of connective tissue (fibroblasts) localised around the lungs. Hyperpolarisation is generated in the stretched lung fibroblasts, which induces generation of slower brain wave activity and parasympathetic shift of ANS [184]. Hyperpolarisation affects the autonomic nervous system by modulating neuronal excitability [191], resting membrane potential [187], and generating rhythmic brain activity [188].

## **9.2 Increased vagal activity**

It is proposed that by stimulating the vagus nerve activity, yoga may enhance parasympathetic output and thereby shift the autonomic balance from primarily

sympathetic to parasympathetic that may buffer the effects of stress leading to positive changes in the cardiovascular, neuroendocrine, and metabolic responses to stress with the resultant decrease in heart rate and blood pressure [172].

It has been proposed that the positive effects of yoga may be mediated by increased vagal activity and consequent reduction in cortisol. This may likely happen via stimulation of dermal and/or sub dermal pressure receptors that are innervated by vagal afferent fibres, which ultimately project to the limbic system and also hypothalamic structures involved in regulating cortisol secretion. These pathways are supported by anatomical studies indicating that baroreceptors and mechanoreceptors within the dermis (i.e. Pacinian corpuscles) are innervated by vagal afferent fibres. Yoga may thus increase vagal activity via stimulation of pressure receptors and cause decrease in cortisol levels [192]. Vagal stimulation promotes down regulation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) [168, 172]. As a result there is a decrease in the release of cortisol and catecholamines leading to reduction in the heart rate and systolic and diastolic blood pressure [193].

In addition, tactile sensory stimulation is conducted through the vagal afferents directly to medulla oblongata in the nucleus of the solitary tract (NTS). Axons from NTS then project to the dorsal motor nucleus of the vagal nerve and the PVN neurons containing oxytocin that mainly influence the NTS regulation of the heart rate and indirectly the blood pressure [194]. Initial studies indicate stress-reducing effects of oxytocin in humans, as increased levels of oxytocin serve to suppress both sympathetic arousal and HPA axis responses to stress [195]. Many studies in humans found support for a negative relationship between basal plasma oxytocin levels and norepinephrine, blood pressure, and heart rate [196].

In studies employing 'Sudarshan Kriya Yoga', a yogic breathing technique, it was found that physiological responses to stress improved through mechanisms involving both afferent vagal activity (altering CNS behaviours) and efferent vagal activity, as well as through decreased chemoreflex sensitivity and improved baroreflex response [197, 198]. In another study it was found that long term practice of yogic breathing enabled body to tolerate exercise induced higher levels of carbon dioxide by decreasing chemoreflex sensitivity mediated via vagus nerve [199]. It has been proposed that adaptation of peripheral/central chemoreceptors to chronic carbon dioxide retention or adaptation of pulmonary stretch receptors to a habit of slow respiration may increase vagal afferent discharge to the brainstem centre NTS. Vagal nerve afferents synapse in the medulla on the nucleus tractus solitarius (NTS), which in turn communicates to the thalamic nuclei via parabrachial nucleus (leading to modulatory effects on cerebral cortex) and the limbic system. Through the limbic system directly or indirectly through subcortical areas, the neuroendocrine outputs are then modulated, resulting in the reduction of cortisol and increase in oxytocin, and prolactin secretion. These vagal effects are physically and emotionally calming and help in alleviation of stress [200, 201].

### **9.3 Restoration of baroreflex sensitivity**

The arterial baroreflex acts to buffer acute changes in blood pressure by reciprocal modulation of sympathetic and parasympathetic activity that controls the heart and vasculature [202]. Baroreflex sensitivity indicates cardiovagal adaptability allowing greater responsiveness and sensitivity to changing environmental demands [172]. Vagal stimulation increases heart rate variability (HRV) and baroreflex sensitivity [203]. HRV is a cyclic variation in the beat-to-beat interval that results from the tonic firing of cardiac-vagal efferents originating in the medulla. High HRV and baroreflex sensitivity are generally considered to indicate cardiovagal adaptability and sympathovagal balance [203].

Yoga breathing exercises and postures are known to have immediate beneficial effects on heart rate variability and baroreflex sensitivity with reductions in heart rate and blood pressure [171, 172, 182, 204]. These effects are thought to reflect direct stimulation of the vagal nerve [171, 172].

Practice of yogic postures has been shown to restore baroreflex sensitivity leading to blood pressure reduction [171]. It is suggested that strong mechanical pressure at the neck by some yogasanas like 'halasana' and 'sarvangasan' can increase arterial pressure (locally) so as to stimulate carotid baroreceptors to activate baroreceptor reflex mechanism leading to reduction in the heart rate and fall in the blood pressure via parasympathetic stimulation as in relaxation technique [205].

In a study conducted in the patients of essential hypertension (EH), it was found that at the end of 3 weeks of yoga course, the head-up and head-down tilt yogasanas restored baroreflex sensitivity to normal and reduced blood pressure significantly. It was suggested that once the sensitivity of baroreceptor mechanism was restored, it corrected all other neurohormonal malfunctioning, which was evident from the reduction in sympathetic activity, blood catecholamines, plasma rennin activity [171].

In another study exploring the effects of aerobic exercise training and yoga, on the baroreflex sensitivity in sedentary, healthy, normotensive elderly persons, it was found that, after 6 weeks of yoga training, the heart rate decreased in yoga group [204]. There was increased alpha-index at High Frequency (HF) reflecting parasympathetic activity but alpha-index at mid frequency (MF) (reflecting sympathetic activity as well) was not increased. However, short-duration aerobic training did not modify the alpha-index at MF or at HF in aerobic group [204].

Besides yogasanas, yogic breathing is also known to increase baroreflex sensitivity. In a study investigating the effect of a single session of slow breathing (6 breaths/minute) in healthy subjects, there was increased baroreflex sensitivity and reduction in chemoreflex sensitivity [206]. This seemed to occur through a relative increase in vagal activity and a corresponding decrease in sympathetic activity. The increase in tidal volume could be responsible for these autonomic changes through a reduction in sympathetic activity or via the Hering-Breuer reflex. Reduced sympathetic activity may be linked to a reduction of chemoreflex overactivity due to the reciprocal influences of the baroreflex and chemoreflex [207].

In yet another study on the patients of essential hypertension, slow breathing increased baroreflex sensitivity and reduced sympathetic activity and reduced chemoreflex activity, suggesting a potentially beneficial effect of yogic breathing technique in hypertension [208]. It has been proposed that slow breathing may enhance baroreflex sensitivity through increased vagal activity and decrease in sympathetic activity. Besides this, slow breathing may also cause increase in tidal volume and activate Hering-Breuer reflex, an inhibitory reflex triggered by lung stretch receptors and mediated by vagal afferents, which may increase baroreflex sensitivity. It has been also suggested that slow breathing may increase oxygen absorption that follows increased tidal volume, this may cause reduction in chemoreflex sensitivity, which in turn may result in increased baroreflex sensitivity via their reciprocal relationship [206–208]. It has also been proposed that, the nucleus tractus solitarius (NTS) acts as an integrating centre for baroreflex, chemoreflex and Hering-Breuer reflex and plays an important role in the effect of breathing on cardiovascular modulation and blood pressure reduction. However, the exact mechanism of such integration is not clear [209].

#### **9.4 Action of yoga on GABA**

GABA is essential as a negative regulator of neuronal excitability in the PVN, thus mediating the amplitude and the duration of the stress response [210]. One of the major mechanisms responsible for inhibition of HPA axis is the direct neural

inhibition of PVN neurons by the neurotransmitter GABA [210, 211]. The neuro-circuitry data suggest that GABA-containing pathways might comprise a key component of the abnormalities in the HPA axis seen in human stress pathology [12]. It is suggested that impaired GABAergic control of PVN neurons may contribute to the elevated sympathetic drive in hypertension [212].

Yoga may be modulating HPA axis and SNS response at the level of PVN by its effect on GABA system. It has been shown that practice of yoga asanas results in significant increase in brain GABA levels especially in thalamus [213]. It is suggested that increase in brain GABA levels following yogic intervention may be due to the ability of yoga practices to increase the activity of parasympathetic nervous system (PNS) by stimulating vagal afferents [213, 214]. Inhibitory influences from thalamus over the stress axis probably may be acting by way of BST-GABAergic inputs to PVN [215].

Thus, the beneficial effects of yoga appear to be mediated through several mechanisms including down regulation of HPA axis and sympathoadrenal system, stimulation of vagus to shift the autonomic balance towards parasympathetic dominance, enhancement of baroreflex sensitivity, and increase in brain GABA levels so as to inhibit PVN, the integrator area of stress signals.

## 10. Conclusion

Stress disturbs homeostasis of the body, which results in a series of neuroendocrine and behavioural responses aiming to cope with the challenges evoked by the stressors. However, chronic exposure to stressors can turn the protective adaptive responses into self-perpetuating vicious cycle of deleterious effects on various systems of the body, including cardiovascular, renal, immune, and nervous system, which finally culminates into pathological conditions like essential hypertension. Yogic intervention exerts its beneficial effects by acting through several different mechanisms and modulates neuro-endocrine control of stress response and cardiovascular behaviour. Thus, yoga has two-way action, at one level it tones down neuro-humoral response to stress and at another level, it brings about improvement in the cardiovascular indices in essential hypertension.

## Conflict of interest

The author declares that he does not have any conflict of interest.



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