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Understanding stress: Neurobiology, mediators and diseases

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ABSTRACT

Stress is a state of threatened homeostasis which mobilizes a composite spectrum of adaptive physiologic and behavioral responses with an aim to restore the homeostasis of the body. Stress is initiated by diverse type of adverse stimuli and responses to the stress include activation of the sympathetic nervous system, glucocorticoid secretion and emotional behaviours. Deregulation of the hypothalamic-pituitary-adrenal (HPA) axis is the hallmark of complex and interrelated changes triggered in the body in response to stress. Persistent stress is associated with different type of diseases such as anxiety, mood disorders and other neuropsychiatric diseases; skin diseases such as psoriasis, urticaria, alopecia areata and atopic dermatitis; gastrointestinal tract diseases such as peptic ulcer, irritable bowel syndrome; inflammatory disease such as rheumatoid arthritis; cardiovascular diseases such as cardiomyopathy and acute coronary syndrome. The present review discusses the role of different stress mediators and different type of diseases resulting due to stress.

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KEYWORDS

Stress;
Steroids;
Neuropeptides;
Diseases;
Hypothalamic-pituitary-adrenal axis.

INTRODUCTION

Stress has been defined as a state of threatened homeostasis which mobilizes a composite spectrum of adaptive physiologic and behavioral responses with an aim to restore the challenged body homeostasis[1]. Although mild stress enhances the immune response and prevents infections, yet the prolonged stress seems to play a pathogenic role in depression and neurodegenerative disorders[2]. Behavioral stress is a main risk factor for many diseases including cardiovascular, metabolic and neuropsychiatric diseases[3]. Deregulation of the stress response can precipitate psychiatric diseases, in particular depression[4]. Deregulation in the hypothalamic-pituitary-adrenal axis (HPA) axis has been associated with upper body obesity and may be the causal link between conditions such as maternal malnutrition and sleep deprivation with metabolic disease[5]. Exposure of rodents to various stress protocols produces many behavioral, neurochemical and neuroendocrine changes that are also observed in humans[6-8]. The animals subjected to chronic stress are used as models of psychiatric pathology, while the acute stress models help in dissecting the molecular and cellular mechanisms involved in stress pathology[9]. The central neuroendocrine system is responsible for the control of homeostatic processes in the body including reproduction, growth, metabolism and energy balance

as well as stress responsiveness. The neuroendocrine system links the brain and peripheral endocrine organs[10]. Stressors have been reported to activate two primary physiological systems, the sympathetic-adrenomedullary system and the HPA axis. Activation of the sympathetic-adrenomedullary system leads to a rapid release of epinephrine (EPI) and norepinephrine (NE) from the adrenal medulla that mobilizes metabolic resources necessary for the fight-or-flight response[11]. The HPA axis is a neuroendocrine system that regulates the body's response to stress and has complex interactions with brain serotonergic, noradrenergic and dopaminergic systems. The hypothalamus derived hormones such as oxytocin and prolactin are documented as potential candidates for the regulation of behavioral and physiological stress responses in the brain[12]. Stressors have also been shown to modulate the secretion of interleukin-6 (IL-6) which is a potent activator of the HPA and appears to play a pathogenic role in stress[13]. Corticotropin-releasing hormone and vasopressin act synergistically to stimulate the secretion of adrenocorticotropic hormone (ACTH) that in turn stimulates the biosynthesis of corticosteroids such as cortisol from cholesterol. Cortisol, the final hormone of this axis, affects metabolic, cardiovascular and central nervous systems both acutely and chronically[14]. Cortisol is a major stress hormone and produces diverse effects on many tissues by acting on mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) in the brain. Glucocorticoids produce behavioral changes and an important target of glucocorticoids is the hypothalamus, which is a major controlling center of the HPA axis[15]. Stress-induce release of glucocorticoids that in-turn act in the periphery and in the brain to bring different changes in the body. MR expression is associated with a neuroprotective phenotype, whereas GR activation is implicated in the induction of an endangered neural phenotype and the opposite actions are most evident in hippocampus, where these receptors are predominantly present. Stress has also been reported to produce an increase in adrenomedullin levels suggesting a regulatory or protective role for adrenomedullin in countering HPA activation. Hippocampus has an overall inhibitory influence on the activity of the HPA axis and it has been suggested that efficient learning and adequate stress response depend on the appropriate functioning of the axis brought by coordinated activation of MR and GR in this region[16]. The present review discusses the neurobiology of different stress mediators along with different type of diseases resulting due to stress.

TYPE OF STRESS RESPONSE

Acute stress response

The acute phase response is a complex systemic early-defense system activated by trauma, infection, stress, neoplasia and inflammation[17]. Acute stress induces rapid changes in the release of neurotransmitters, hormones and cytokines that are adaptive, but may become damaging if the stress response is inadequate or excessive. Inappropriate stress response acts as a trigger, which may produce a vulnerable phenotype in genetically predisposed individuals and increase the risk for mental illness[6]. A number of studies have suggested that acute stress is associated with an increased excitatory amino acid transmission in areas of the forebrain[3]. Acute stress has also been shown to induce sympathoadrenergically mediated increase in chemotaxis and adhesion molecules expression, thus promoting immune cells migration to sites of infection and/or inflammation, while the chronic stress has reported to impair this mechanism[18]. The medial prefrontal cortex (mPFC) and locus coeruleus (LC) has been reported to play an important role in modulating HPA responses to acute emotional stress[19-21]. An acute physical or psychological stressor activates two main physiological systems, the HPA axis and the sympathoadrenal system, resulting in a range of hormonal, cardiovascular, cognitive and emotional responses, which may vary independently of one another. Many drugs of abuse including nicotine and alcohol have also been shown to stimulate the same physiological systems as acute stressors[22-24].

Chronic stress response

Chronic stress leads to cumulative changes in the brain that are not seen after acute stress. Such changes indicate compromised brain plasticity and increased vulnerability to neuropathology[25]. It has been associated with detrimental or maladaptive neuroendocrine and immunological changes[26] which are precipitated by pronounced enhancement of central stress excitability, marked by sensitization of HPA axis responses and an increased ACTH biosynthesis in the paraventricular nucleus of the hypothalamus (PVN)[27]. The medial

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amygdaloid nucleus (MeA) is necessary for the development of maladaptive pathological changes caused by prolonged stress exposure[28]. Chronic stress produces numerous adaptations within the HPA axis that persist even after cessation of chronic stress[29]. Adaptation refers to the process whereby the response to a stressor changes with repeated exposure. For example, an increased corticosterone observed after acute exposure to a stressor dampens after repeated exposure, though it is the prolonged release of corticosterone that is thought to be responsible for chronic stress-induced damage[30]. Deregulation in the HPA axis has been associated with upper body obesity. In addition to systemic effects, changes in local cortisol metabolism in adipose tissue may also influence the risk for obesity[5]. The studies have shown change in the expression and distribution of different proteins in the brain regions including the cortex and hippocampus[31].

STRESS MEDIATORS

Stress means an actual real or potential threat that produces immediate changes in behavior as well as changes in the future behavior. This has been shown to modulate the neuronal functioning at several steps of CNS including learning and memory, decision making, autonomic, hormonal and emotional responses[32]. The different types of stressors produce different types of responses. For example, physical stressor (blood loss, trauma and cold) produces changes in brain stem and hypothalamic regions[33,34] whereas psychological stressors (social embarrassment and examinations) primary involve stress mediators in brain regions that helping in learning and memory (the hippocampus), emotions (the amygdala and the prefrontal cortex), and decision making (the prefrontal cortex)[6,35,36].

Three main classes of stress mediators and their contribution to the brain's stress response are discussed below:

Monoamines

The release of monoamines including serotonin, noradrenaline and dopamine has been shown to be increased after the stressful events in the specific neuronal populations[37-40]. Serotonin is mainly released in post stress anxiety and dopamine is released in prefrontal cortex during moderate stress[37]. The release of monoamines is triggered directly by the brain circuits involved in stressful event or indirectly through activation of sympathetic nervous system[34,36]. The activation of monoaminergic system depends on factors such as sex (90), the time of day and the controllability of stressors[39]. For example, in uncontrollable stress the activation of raphe neurons (produce serotonin) by the shock exposure is more prominent[39,41]. The release of monoamines is induced within minutes after the onset of the stressor[42] and outlasts the exposure of stressor duration. An increased release of monoamines after stressful stimuli has been demonstrated in hippocampus, the prefrontal cortex, the amygdale, the nucleus accumbens and in many other brain areas. However, the spatial distribution of the resulted release depends on the affinity and monoamines receptor subtypes distribution. Thus, the combination of affinity, distribution of receptors and release site provides a single stress mediator with different functions and multiple niches. The enhanced levels of noradrenaline help in processing of sensory information to a more general scanning of the environment, which may provide solution to challenging conditions[43]. Thus, overall the monoamines improve behavior strategies that help the animal to survive in initial phase of stress.

Neuropeptides

The neuropeptides are released from specific neuronal populations by stress and contribute in induction of stress by activating multiple receptors[44,45]. These neuropeptides have been shown to act on peripheral receptors also. During stress response, the corticotrophin releasing hormone (CRH) is released from axon terminals in hypothalamic median eminence, and act on pituitary receptors[46]. It is now also explicit in neuronal population in the amygdale[44,46], the hippocampus[47] and the locus coeruleus[48]. The peptide produces neuromodulatory effects on target neurons within seconds after release of peptides[49,50] through two G protein-coupled receptors, CRHR1 and CRHR2. CRH receptor occupancy affects neuronal firing patterns[49,50], gene expression[44] and behaviour[44,51] in a dose and context-dependent manner. The stress induced activating action of CRH has been mediated through binding to CRHR1[23,44,48]. In addition, studies in mice suggest that CRHR2 binding could exert effects at longer timescales and might function to shut down the stress

response[51,52]. Stress-induced over-activation of CRH/ CRH-R1 produces rapid deleterious effects on dendritic spine morphology and thus, impairs synaptic plasticity and spatial memory in chronic stress subjected animals[53]. The dual role of CRH on stress-induced cognitive changes has been described. For instance, the release of CRH in central nucleus of the amygdale during acute stress increases memory strengthening[54,55]. The modest stress-induced CRH release from the hippocampal interneurons[56] primes long-term potentiation[57] and memory improvement[58] while severe stress induces large amount of CRH release from hippocampus leading to hyper-excitability and seizures, and rapid loss of dendritic spines in CA3 pyramidal cells[56]. Severe stress-induced large amount of CRH release from hippocampus may lead to hyper-excitability and seizures, and rapid loss of dendritic spines in CA3 pyramidal cells[23,56].

In addition to CRF, the mammalian CRF-peptide family contains urocortin 1 (UCN-1), Urocortin 2 (UCN-2) and Urocortin 3 (UCN-3). Urocortin 1 has a high affinity for both $CRFR_1$ and $CRFR_2$; while UCN-2 and UCN-3 have a high affinity for $CRFR_2$. The urocortins (UCN1, 2 and 3) are the members of CRH neuropeptides family which can bind to CRH receptors and act in spatial domains. The role of UCN1-expressing neurons in the non-preganglionic Edinger–Westphal nucleus in the brainstem in stress adaptation has been reported[59]. The role of UCN-2 (a selective $CRFR_2$ agonist) in 'stress-coping' responses in the brain has been reported in mice and altered expression of genes in triple urocortin knock out mouse model differentiate the response to acute stress and indicating the urocortins as essential factors in the stress-recovery process[60]. Urocortin-3, a specific ligand for the type-2 corticotropin releasing factor receptor, modulates the functions of septal and hypothalamic nuclei, responsible for anxiety-like behavior and metabolic functions[61]. Arginine vasopressin (AVP), also known as vasopressin, argipressin or antidiuretic hormone (ADH), is a neurohypophysial hormone found in most mammals and it shows its action by acting on $AVPR_{1A}$, $AVPR_{1B,}$ $AVPR_2$ and $AVPR_3$ receptors. The role of brain $AVPR_1$ in mediating the enhanced cardiovascular responses including mean arterial blood pressure and heart rate in response to acute stress in chronically stressed rats has been described[62]. $AVPR_{1A}$'s role in social recognition is particularly important in the lateral septum, as using viral vectors to replace inactivated $AVPR_{1A}$ expression rescues social recognition and increases anxiety-related behavior[63] However, conflicting results have been found in another study[64]. In the hypothalamic region, vasopressin interacts with CRH and stimulates ACTH release from the pituitary in response to stress[65]. In the amygdala, the excitatory actions of vasopressin may contribute to the behavioral stress response like emotional memory and anxiety[1,66].

Orexin is the one of the essential modulators required for orchestrating the neural circuits controlling autonomic functions and emotional behaviors i.e., linking the emotional stress to the autonomic functions[67]. Orexin neurons are the pivotal link between the conscious and unconscious brain functions. The preclinical studies have shown the involvement of orexins in the regulation of stress, affectivity and addictive behavior. The role of NPY in the stress response has been investigated in both clinical and preclinical studies[68]. The modulation of NPY levels in various animal models implicates the role of NPY in depression-like behaviors. The animal studies have shown that activation of NPY Y1 receptor or deletion/blockade of Y2 receptor subtype is associated with antidepressant-like activity in acute models of depression[69,70]. The role of Y4 receptors in the regulation of behavioral homeostasis and depression-like behaviors has also been documented[71].

Extensive studies were carried out on the involvement of the CCKergic system in anxiety-, panic- and stress-related behaviour. It was found that stress resulted in a significant decrease in the extracellular levels of CCK-like immunoreactivity in the hippocampus, and partially suppressed the increase obtained during the acquisition phase of memory, suggesting that the CCKergic system in the hippocampus is involved in stress-induced impairment of memory. CCK-B receptors play a role in modulating activity within the hypothalamic–pituitary adrenal (HPA) axis, implicating that CCK may be a modulator of emotional behavior and stress responsiveness[72]. Ghrelins, a pleiotropic hormone secreted from endocrine X/A-like cells of the stomach and also acts as central orexigenic hormone[73]. An increased ghrelin levels tend to produce anxiolytic- and antidepressant-like responses in the elevated plus maze and forced swim test[74]. Ghrelin regulates the glucose metabolism, appetite, body weight and prevents

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excessive anxiety under conditions of chronic stress. Ghrelin knockout (Ghr-/-) mice are more anxious after acute restraint stress as compared to wild-type. Very recently, it has been shown that ghrelin reduces anxiety after acute restraint stress in mice by stimulating the HPA axis at the level of the anterior pituitary[76].

The role of other neuropeptides such as dynorphin, oxytocin, galanin and substance P has also been described in stress[44].

Steroids

Corticosteroids are secreted in a rhythmic and circadian fashion in the body and stress triggers the release of a large amount of corticosteroids that is superimposed on these rhythms. In the mammalian brain, corticosteroid hormones primarily act through mineralocorticoid and glucocorticoid receptors (MRs and GRs, respectively). GRs receptors are only partially occupied under basal conditions and become more occupied when corticosteroid levels are increased after stress. The distribution of these two types of receptors in brain is different[6]. GRs are ubiquitously expressed in the brain, but they are highly expressed in the hippocampus, the lateral septum and the paraventricular nucleus (PVN). MRs are highly expressed in the lateral septum and in neurons of the hippocampal formation and moderately expressed in subnuclei of the amygdala, the hypothalamic PVN and the locus coeruleus. Thus, the MRs distributions overlaps with distributions of CRHR1[77]. These regions are involved in the cognitive, emotional and neuroendocrine processing of stressful events[36]. Corticosteroid receptors, on binding of the hormone, translocate to the nucleus, where they act as regulators of gene transcription[78]. In the hippocampus, MR activation is a prerequisite for maintaining the ongoing information flow, whereas activation of GRs during stress causes a delayed suppression of neuronal excitability and synaptic plasticity[7,79] and provide 'negative-feedback regulation' of behavioral aspects of the stress response. Furthermore, the suppression of synaptic plasticity by GRs could serve to protect the stress-related information that is being consolidated after stressful stimuli.

NEUROBIOLOGY OF STRESS

The principal physiological responses of stress are mediated by the sympathoadrenal system, and the hypothalamo-pituitary-adrenal axis.

Sympatho-adrenal/Sympatho-neural system

The autonomic nervous system has been documented to control numerous systems including sleep, gastrointestinal, cardiovascular, respiratory, renal and endocrine[80,81]. The activation of the sympathoneural system represents one of the key components of the stress response. The sympathetic nervous system is one of the major pathways involved in immune-neuroendocrine interactions[82]. Activation of the sympathetic nervous system is essential for adaptation to environmental stressors and in maintaining homeostasis. However, these reactions may also turn into mal-adaptation associated with a wide spectrum of stress-related diseases[83]. The activation of the sympathoadrenal system functions to reduce blood flow to gastro-intestinal system and reproductive organs and to mobilize energy to the brain, heart and muscles[84]. This mechanism has been evolved to create quick compensatory changes in homeostasis for intense physical activity by increasing the capacity of the 'fight or flight' reaction and therefore, promote survival. The sympathetic nervous system and adrenal catecholaminergic tissue act to prepare an animal for "fight or flight" by release of catecholamines into synapses and plasma[85]. The activation of the sympathoadrenal system evokes the release of noradrenaline and neuropeptide- Y from postganglionic nerve terminals, while preganglionic innervation of the adrenal medulla results in an increased secretion of adrenaline and dihydroxyphenylaline (DOPA)[86].

Hypothalamic-pituitary-adrenal axis (HPA axis)

The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine system that regulates the body's response to stress and has complex interactions with brain serotonergic, noradrenergic and dopaminergic systems[15]. It has a fundamental role in adaptation of an organism to homeostatic challenge and is considered as energy regulator because it is responsible for controlling all of the hormonal and neuronal activity along with mineral homeostasis[87]. Glucocorticoids produce behavioral changes and one important target of glucocorticoids is the hypothalamus which is a major controlling center of the HPA axis[15]. Dopamine is involved in the maintenance of post-stress activation of the HPA axis and is potentially important because the actual

pathological impact of HPA activation is be related to the area under the curve of plasma glucocorticoid levels[88]. Glucocorticoids alter synaptic structure and function in the brain regions to alter behaviour, learning and memory[89]. Sensory information reaches the cortex via the thalamus and is conveyed to the central amygdaloid nucleus of the amygdala[90]. It responds by providing the stimulus to cortico-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus to increase the secretion of principal neuropeptide CRH and arginine vasopressin (AVP) into the hypophyseal portal bloodstream. These secretions are transported to the anterior pituitary gland[91]. The corticotrophin producing cells of the anterior pituitary synergise CRH and the AVP through CRH-RI and VIb receptors, respectively to increase expression of the adreno-corticotropin hormone (ACTH) precursor, and further promote the release of ACTH into the systemic circulation[92]. ACTH stimulates the zona fasciculata cells of the adrenal cortex to release synthesized glucocorticoid (cortisol in humans) and mineralocorticoid hormones (principally aldosterone)[93,94]. Glucocorticoids control the termination of the stress response via inhibitory control of the production and release of CRH and ACTH at the level of the hypothalamus and pituitary respectively[8]. In addition, inhibition of the ACTH response occurs through the glucocorticoids binding to receptors in the hippocampus, which control CRH production and limiting the period of exposure to the stress response, therefore minimizing the catabolic immunosuppressive and anti-reproductive effects of glucocorticoids[95].

STRESS INDUCED DISEASES

Skin diseases

Skin is continuously exposed to multiple exogenous and endogenous stressors[96]. Psychological stress adversely affects the immune system and aggravates various skin diseases such as psoriasis, urticaria, alopecia areata and atopic dermatitis[97]. Many cutaneous disorders are adversely affected by psychological stress, but the responsible mechanisms are poorly understood. The recent studies have demonstrated that psychological stress decreases epidermal proliferation and differentiation, impairs permeability barrier homeostasis, and decreases stratum corneum integrity. Psychological stress also increases the production of endogenous glucocorticoids, which adversely affect epidermal structure and function in psychological stress[98]. Skin barrier is altered by stress through increased cortisol level, which leads to decrease in lamellar body secretion and down-regulation of epidermal expression of antimicrobial peptides (beta-defensin and cathelicidin)[99]. The nerve growth factor (NGF) and several cytokines have also been identified as important players of the stress response. The circulating NGF levels are increased in patients with inflammatory skin diseases, such as psoriasis[100]. Skin mast cells produce CRH and express CRH receptors type 1[66,101] that are activated by neuropeptides such as peripheral CRH, substance P and calcitonin gene-related peptide (CGRP) in response to stress[96]. Antipsychotic and anxiolytic agents have been shown as effective agents for stress-aggravated inflammatory skin diseases by inhibition of mast-cell degranulation[102].

Psoriasis is a mainly T helper-type 1 (TH (1)) cell mediated chronic inflammatory skin disease characterized by epidermal hyperproliferation and psoriatic plaques. There have been evidences showing that stress trigger psoriatic eruption[103]. Psychological stress causes phenotypic changes in circulating lymphocytes and is regarded as an important trigger of the Th1-polarized inflammatory skin disease psoriasis. Stress-induced increase of CD3+ T lymphocytes has been reported in patients with psoriasis. Analyses of T-cell subsets have revealed that this increase is also observable for cytotoxic CD8+ T lymphocytes and CLA+ CD3+ lymphocytes. The total number of circulating NK cells (CD16+, CD56+) has been shown to increase immediately after stress, whereas the patients with psoriasis an increase in CLA+ NK cells has been documented[104]. Atopic dermatitis is a chronic inflammatory skin disease mainly triggered by TH (2)-dependent inflammatory processes. Stress increases parameters of atopic dermatitis such as eosinophil infiltration, vascular cell adhesion molecule-positive blood vessels and epidermal thickness. The dramatic pathologic exacerbation is associated with increased neurogenic inflammation including degranulated mast cells, interstitial neuropeptidergic dense core granules, mast cell apoptosis and endothelial gaps[105]. The different neuropeptides and neurotrophins have been reported to play an important role in stress-induced neurogenic in-

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flammation in connection with nervous and immune system.

Gastrointestinal tract diseases

Stress has been shown to affect the GIT motility, faecal transit, visceral pain sensitivity, the permeability and function of the gut epithelium[106]. Physical and psychological stresses have been widely accepted as triggers or modifiers of the clinical course of various gastrointestinal disorders such as peptic ulcer, irritable bowel syndrome or inflammatory bowel disease[107,108]. The animals exposed to prolonged stress develop gastric ulceration, enhanced colon motility with depletion of its mucin content and signs of physiological and behavioral arousal[109]. Irritable bowel syndrome (IBS) is a common health issue that is characterized by abdominal pain, abnormal bowel movements, altered visceral perception[110]. Stress can also synergize with other pathogenic factors such as Helicobacter pylori, nonsteroidal anti-inflammatory drugs or colitis-inducing chemicals to produce gastrointestinal disease[107]. Stress has been documented to stimulate exocrine pancreatic secretion through cholinergic pathways, and release of trypsin in these conditions may be responsible for colonic barrier alterations by increasing colonic paracellular permeability (CPP) through the activation of protease-activated receptor-2 (PAR2)[108]. Repeated stress challenges the mucosal integrity and the activity of mucin-producing cells[111]. An increased epithelial permeability after psychological stress has been shown in all regions of the gastrointestinal tract and is mediated by adrenal corticosteroids. Stress-induced increase in epithelial permeability has been reported to disappear after adrenalectomy or pharmacologic blockade of glucocorticoid receptors[112].

Stress has been reported to modulate gastrointestinal motility through central mechanisms including corticotropin-releasing-factor, and this process requires the integrity of autonomic neural pathways. Apart from brain, both CRF receptors and ligands are also widely expressed in the colon and the ileum of humans and rodents, and stress modulates their expression[113]. Inflammation and stress have been associated with colorectal hypersensitivity in functional gastrointestinal disorders[114]. Recently chronic stress has been reported to increase plasma norepinephrine and sensitizes colon-specific dorsal root ganglion (DRG) neurons by increasing expression of nerve growth factor (NGF) in the colon wall. The blockade of alpha and beta adrenergic receptors has been reported to prevent the stress-induced visceral hypersensitivity and increased expression of NGF in the colon wall[115].

Inflammatory disease

Stress influences circulating inflammatory markers, and these may mediate the deleterious effects in inflammatory conditions such as rheumatoid arthritis[116]. Stress protocols (physical, psychological or mixed) show a pro-inflammatory response in the brain and other systems mainly characterized by a complex release of several inflammatory mediators such as cytokines, prostanoids, free radicals and transcription factors. The anti-inflammatory pathways are activated in the brain in response to stress, and these constitute a possible endogenous mechanism of defence against excessive inflammation[117]. Psychological stress has been associated with an increase levels of inflammatory cytokines such as interleukin-1beta (IL-1beta), IL-6 and tumor necrosis factor alpha (TNF-α) in the brain[118]. Psychosocial stress alters susceptibility to infectious and systemic illnesses and may enhance airway inflammation in asthma by modulating immune cell function through neural and hormonal pathways. Stress activates the hypothalamic-pituitary-adrenal axis and release of endogenous glucocorticoids may play a prominent role in altering the airway immune hypersensitivity[119]. Hypothalamic-pituitary-adrenal axis activation influences eosinophilic inflammation through specific sequences of compartmental activation and thereby timing effects are evident on cellular recruitment pattern during the allergic reaction[120].

Mu-Opioid receptors have been shown to be involved in the shift of the immune system toward a Th2-predominant response caused by psychological stress. Mu-Opioid receptors in the CNS are involved in psychological stress-induced aggravation of allergic airway inflammation[121]. Chronic restraint stress induces inflammation, demyelination, and axonal degeneration in CNS. Capsaicin-sensitive sensory fibers play a key role in stress-induced visceral hypersensitivity and the mast cells play an important role in the generation of stress-induced colon inflammation[122]. The intestinal barrier is formed by enterocyte membranes, tight junctions, secreted mucus, and immunologic factors, such as tissue

macrophages. Dysfunction of this barrier can be caused by different types of stressor such as (physiological, pathological, psychological, pharmacological) and can lead to increased intestinal permeability. Increased permeability to endotoxin, a component of the walls of gram-negative bacteria, causes local or systemic inflammatory reactions[61]. Acute stress is involved in the regulation of local pro-inflammatory responses in chronic inflammation, i.e., gingivitis. In vivo study has demonstrated that psychological stress alters the local concentrations of IL-8 under conditions of chronic inflammation[123]. Inflammatory cytokines and the cholinergic system have been implicated in the effects of stressors on mood and memory; however, the underlying mechanisms involved and the potential interrelationships between these pathways remain unclear. Exposure to a surgical stressor induces a reciprocal up-regulation of acetylcholinesterase and pro-inflammatory cytokines, which are involved in regulating the surgery-induced mood and memory disturbances[124]. Stress exacerbates allergic dermatitis (AD) via substance P (SP) -dependent cutaneous neurogenic inflammation and subsequent local cytokine shifting[105].

Cardiovascular disease

Stress is an important risk factor for cardiovascular disease. Acute restraint is an unavoidable stress situation that evokes marked and sustained cardiovascular changes, which are characterized by elevated blood pressure and increased heart rate. The combination of prenatal stress followed by restraint stress results in reversible depression in both systolic and diastolic function as well as defective beta-adrenergic receptor signalling[122]. Mental stress can significantly affect ventricular repolarization, which could potentially trigger arrhythmias[56]. Stress has been documented to induce cardiomyopathy, also called transient left ventricular (LV) apical ballooning syndrome, broken heart syndrome, ampulla cardiomyopathy. Cardiomyopathy is characterized by a transient and reversible left ventricular dysfunction and shows clinical similarities with the acute coronary syndrome. The disease mimics myocardial infarction, but there is an absence of significant coronary artery disease[125,126]. The reduction of estrogen levels following menopause may also be the cause of takotsubo cardiomyopathy both by indirect action on the nervous system and by direct action on the heart. Immobilization stress in rats has been shown to produce the electrocardiographic and left ventriculographic changes similar to that is takotsubo cardiomyopathy. Estrogen supplementation has been shown to partially attenuate these cardiac changes and downregulate c-fos mRNA expression in the adrenal gland and the heart, suggesting an increased estrogen attenuates stress-induced hypothalamo-sympathoadrenal outflow from the central nervous system to the target organs. Estrogen treatment has also been shown to upregulate the levels of cardioprotective substances, such as atrial natriuretic peptide and heat shock protein 70 in the heart[127]. Emotional stress-induced acute coronary syndrome is mediated by increased inflammatory and vasoconstrictive mediators[128]. Emotional stress trigger acute coronary syndromes in patients with advanced coronary artery disease (CAD), although the mechanisms involved remain unclear[129]. The proposed mechanisms for catecholamine-mediated stunning in stress cardiomyopathy include epicardial vasospasm, microvascular dysfunction, hyperdynamic contractility with midventricular or outflow tract obstruction, and direct effects of catecholamines on cardiomyocytes[130].

An acute psychological stress can precipitate ventricular arrhythmias and sudden cardiac death in patients with coronary artery disease (CAD). Mental stress-induced myocardial ischemia occurs in a significant percentage of the CAD population. The pro-arrhythmic effects of psychological stress may be mediated through the development of myocardial ischemia[131]. Mental stress-induced blood pressure elevation has been related to cognitive dysfunction in the elderly, and role of calcium channel in stress-induced hypertension in subjects with mild cognitive impairment has been suggested[134].

CONCLUSION

Stress triggers multifold changes in the body and complex set of events involving activation of sympathoadrenal/sympatho-neural system and hypothalamic-pituitary-adrenal axis. The diverse stress mediators including monoamines, neuropeptides and steroids play an important role in bringing the different changes during the state of stress. As a consequence, number of neuropsychiatric diseases such as skin diseases, gastrointestinal tract diseases, cardiovascular and other in-

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flammatory diseases may result due to persistent stress. The understanding of these complex changes may help in development of therapeutic agents to overcome the stress related different disorders.

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