Review Article

Regulation of Stress - Need of an hour to prevent human health

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Abstract

Objective: Stress can be defined as the over all those reactions in our body, which can disturb the normal functioning and physiological equilibrium of body system. The objective of this review is to compile literature related to stress origin and the related research work to reduce stress and stress induced disorders. **Materials and methods**: The all reported work related to this topic was collected from various source e.g. library, online site pubmed, sciencedirect and books. The exhaustive literature was studied and makes critical analysis to summarize the findings. **Results:** Through novel techniques, it is also possible to measure the response of the primary stress systems in a convenient, non-invasive manner. Thus, allowing the research to progress rapidly in the area of stress which is important to improve quality of life. By gaining a thorough understanding of the systems governing stress response, the intervention techniques can be developed to target the over-activation of these systems, decrease stress, and improve health. **Conclusion:** The recent findings concerning stress induced disorders are a solid starting point for much needed future research.

***Keywords*: Stress, antioxidants, stress induced disorders, immune system, regulations

Introduction

In medical terms stress is described as, **"a physical or psychological stimulus that can produce mental tension or physiological reactions that may lead to illness".** Humanbody tries to adjust the different circumstances due to continually changing of surrounding environment, in which the body is put to extra work resulting in "wear and tear". In other words, stress disturbs the body's normal way of functioning. Although, a certain level of stress is healthy and perhaps necessary, high levels of persistent and intense stress can lead to a host of negative outcomes affecting behavioural, social, health and psychological functioning. Many consider stress, a disease that can make one mentally and physically sick. As per stress report (2011), it has been estimated that the economic toll of stress costs the American government more than $200 billion dollars annually in terms of health costs and lost productivity. Although, the current world-wide estimate in managing stress is yet to receive. In order to combat stress-related symptoms and diseases, it is important to understand the mechanism involved in the stress response and to develop the relevant techniques to measure the activation of stress response (Zardooz et al., 2012; De Quervain et al., 1998; Berle et al., 1952).

As per the most widely accepted definitions given by Dr. Richard Lazarus, stress is a dynamic relationship between an individual and his or her environment perceived by the person as demanding or exceeding his or her resources. Stress management is complicated due to its different types viz. acute stress and chronic stress, each type having its own characteristics, symptoms, duration and treatment approaches (Zardooz et al., 2012). Generically, stress can be classified as acute and chronic stress.

Acute Stress: It is the most common form of stress arising from demands and pressures of the recent past and anticipating the same in the near future. Acute stress is thrilling and exciting in small doses, but too much of it is exhausting. Overdoing of short-term stress can lead to symptoms such as psychological distress, high blood pressure, headache and gastric upset etc. Fortunately, acute stress symptoms are recognized commonly because of its short term tenure and it does not cause an extensive damage as associated with long-term stress. The most common symptoms of acute stress are emotional distress, muscular problems including headache, back pain, jaw pain, and the muscular tensions that lead to pulled muscles, tendon and ligament problems, stomach, gut and bowel problems such as heartburn, acidic stomach, flatulence, diarrhea, constipation and irritable bowel syndrome, transient over arousal leads to elevation in blood pressure, rapid heart-beat, sweaty palms, heart palpitations, dizziness, migraine head-ache, cold hands or feet, shortness of breath and chest

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pain.

Chronic Stress: This is the grinding stress that wears people away day after day and year after year which abruptly destroy body and mind which wreaks havoc through long-term attrition. Chronic stress arises when a person never sees a way-out of a miserable situation, unrelenting demands and pressures for seemingly interminable periods of time.In addition the individual gives up searching for solutions. Some chronic stresses stem from traumatic, early childhood experiences that become internalized and remain forever painful whereas some experiences profoundly affect the personality. A view of the world, or a belief system, is created that causes unending stress for an individual wherein the worst aspect of chronic stress is that people get used to it due to its long-term nature (Azbill et al., 1997).

Chronic stress kills through suicide, violence, heart attack, stroke, and even cancer where people wear-down to a final, fatal breakdown. In such cases the physical and mental resources are depleted through long-term attrition as well as the symptoms of chronic stress are difficult to treat and may require extended medical as well as behavioral treatment and stress management (Compas et al., 1997). Response of human body after an exposure to Chronic stress is addressed in **Table 1.**

Table 1 Effect of Chronic stress on human body

Parameter	Effect
Behaviour	Restlessness, Sleep, disturbances/insomnia, Loss of apetite/overeating, Avoidance/ phobias, Agerssion/irritability, Decreased sexual activity, Compulsive behaviour
Emotion	Anxiety, Depression, Anger, Guilt, Suicidal feelings
Sensation	Tension, Headache, Indigestion, Dizziness/feeling faint, Premature ejaculation/erectile dysfunction
Physiology	High Blood pressure/coronary heart disease (angina/heart attack), Diarrhoea/ Constipation/ Flatulence, Lowered immune system, mental disorders

During chronic stress, the body reacts to the stressing agents (stressor's) by exhibiting a stress response. As per Seaward (2012) "Situations, circumstances or any stimulus that is perceived to be a threat is referred to as a stressor, or that which causes or promotes stress". The causes of stress are known as *stressors* which are of different types which can be physical in nature (such as a car accident) or psychological (realizing one's financial trouble) (Luke, 1990).

Physiology of Stress

The physiology of stress is referred as a part of psychophysiology which reflects the fact that a sensory stimulus prompts the stress response that may be processed at the mental level. In other words the term psychophysiology suggests that there is a mind body relationship and supports the theory that many diseases and illnesses are psychosomatic, which means the origin of stress lie in the higher brain centres. The three systems of the body directly involved with the regulation of stress are: The nervous system, the endocrine system and the immune system.

All of which can be triggered by perceived threats. When an individual experiences a stressor, the autonomic nervous system (ANS) and the hypothalamic pituitary adrenal system (HPA axis) are activated.

The Nervous System

The nervous system is divided into two parts: Central nervous system (CNS) and Peripheral nervous system (PNS). The CNS consists of the brain and the spinal cord and the PNS comprising all the neural pathways to the extremities. The human brain is further divided into three levels: the vegetative level, the limbic system and the neocortical level (Robertson, 2005).

The Vegetative level

The lowest level of brain consists of both the reticular formation and the brain stem. The reticular formation or more specifically the fibers that make up the reticular activating system (RAS), is the link connecting the brain to the spinal cord. Stress physiologists also believe that it is the bridge joining the mind and the body as one which functions as a communication link between the mind and the body (Robertson, 2005).

The Limbic system

The second or mid level portion of the brain is called the limbic system. The limbic system is the emotional control center. Several tissue centers in this level are directly involved in the biochemical chain of events that constitute the stress response. The limbic system consists of thalamus, hypothalamus, amygdale and pituitary gland (also known as master endocrine glands).These four glands work in unison to maintain a level of homeostasis within the body.

The Neocortical level: The neocortex is the highest and most sophisticated level of the brain. At this level the cognition (thought process) takes place as well as the sensory information is processed (decoded) as threat and nonthreat. Housed within the neocortex are the neural mechanisms allowing one to employ analysis, imagination, creativity, intuition, logic, memory and organization.

Apart from CNS, the PNS comprises of two individual networks, first of which is somatic network, a bidirectional circuit responsible for transmitting sensory messages along the neural pathway between the five senses and the higher brain centers. These are called the efferent and the afferent neural pathways. The second branch of PNS is influential system involved in the stress response, called as the Autonomic nervous system (ANS). The ANS regulates the visceral activities and vital organs, including circulation, respiration, digestion and body temperature. Activation of the ANS occurs almost immediately following the experience of a stressor to prepare the body to cope with the situation.

The ANS is comprised of two systems with opposing roles: the sympathetic nervous system (SyNS) and the parasympathetic nervous system (PyNS). These two branches of ANS act to maintain the homeostatic balance in the body. When an organism is aroused or stressed, the SyNS is activated and is responsible for the release of regulatory substances associated with the fight or flight response. This SyNS releases the substances called catecholamines, specifically epinephrine (adrenaline) and nonepinephrine (nonadrenaline) at various neural synapses, a series of events occur in several organ/tissues to prepare the body for rapid metabolic change and physical movement. These hormones prepare the body to deal with the challenge by eliciting the in the bady such as: dilating the pupils, accelerating the heart-beat and inhibiting digestion. They prepare the body to engage with or flee from the stressor, and due to this reason, the SyNS is the field of interest to researchers for several years (Robertson, 2005). Fortunately, research has found a non-invasive, more convenient way to measure the activity of the SNS by sampling α-amylase, an enzyme found in saliva that has been thoroughly studied in oral biology. Its primary function is the digestion of carbohydrates, although it has also been identified as the first line of immune defense because it helps to clear bacteria from the mouth. The concentration of α-amylase has been shown to rise during physical and psychological stress, whereas blocking noradrenaline and adrenaline receptors in the brain inhibits the release of α-amylase (Nater et al., 2006).

The level of stress-related increase of α-amylase is correlated with the level of noradrenaline. Even though, these studies do not interpret the direct relationship between α-amylase and level of stress. Hence, α-amylase is considered to be a reliable non-invasive marker of SyNS activation. The sympathetic drive is associated with energy expenditure, a process known as catabolic functioning whereas the parasympathetic drive is responsible for energy conservation and relaxation. This is referred to as anabolic functioning during which body cells are allowed to regenerate. Activation of parasympathetic nervous system releases acetylcholine (ACh), a neurological agent that decreases the metabolic activity and returns the body to homeostasis indicates that the stressful situation is over, and hence the activation of PNS returns the systems of the body back to normal (Nater et al., 2006).

In addition, there are certain neurotransmitters that play an important role in regulating the stress induced disorders. These are glutamate, serotonin, gama amino butyric acid (GABA) and dopamine.

Glutamate is the major excitatory neurotransmitter in the CNS which plays an important role in several physiological functions including learning, memory and developmental plasticity.It has also been implicated in a variety of neurodegenerative disorders. Glutamate is also involved in critical reproductive and neuroendocrine events, such as puberty, gonadotropin pulsatility, the pre-ovulatory gonadotropin surge and reproductive behavior. Hence, a deficit in the glutamatergic system may also participate in the reproductive decline associated with aging (Martin et al., 2006).

Glutamate exerts its effects through binding and activation of two classes of specific receptors, ionotropic glutamate receptor (iGluRs) and metabotropic glutamate receptor (mGluRs). Group I mGluR includes mGluR1 and mGluR5 subtypes, group II includes mGluR2 and mGluR3 subtypes and group III includes the subtypes mGluR-4, 6, 7 and 8. Glutamate and its receptors are found in all key hypothalamic areas critically involved in reproduction and neuroendocrine function. Considerable available data supports an important role for iGluRs in the control of neuroendocrine function (Martin et al., 2006).

Finally, mGluRs selective agonists may have an impact in the treatment of conditions involving chronic stress, such as depression and anxiety disorders by regulating the neuroendocrine stress circuits (Sagara and Schubert, 1998).

Serotonin[5-Hydroxytryptamine (5-HT)] is a monoamine neurotransmitter, biochemically derived from tryptophan, that is primarily found in the gastrointestinal(GI) tract, platelets, and central nervous system(CNS) of humans and animals. It is a well-known contributor to feelings of well-being. The serotonergic system is known to modulate and mediate many of the CNS effects of stress. The effect of stress on central nervous transmitter systems are of biomedical interest because prolonged stress can lead to anxiety disorders and depression (Thierry et al., 1968).

Both stress and anxiety have been related to an activation of the central nervous 5-HT system, and it has been reported that the "stress hormone" corticosterone increases the activity of tryptophan hydroxylase, the rate limiting enzyme of 5-HT synthesis. () Acute stress dramatically affects synaptic plasticity in the hippocampus, prior inescapable stress profoundly and persistently inhibiting the induction of long-term potentiation (LTP) by high frequency stimulation. LTP in the hippocampus provides a model of synaptic memory mechanisms and dysregulation of its induction or maintenance which may be an important aspect in stress-related psychiatric disorders such as depression where normal hippocampal function is often impaired (Graeff et al., 1996; Diamond and Rose, 1994).

It is well established that stress leads to cause changes in the serotonergic system. In order to gain a better understanding of the effects of recurrent stressful experiences on the serotonergic system, changes in the 5HT receptor system resulting from different periods of psychosocial stress (PSS) were analyzed and it was found that the dynamic 5-HT-receptor changes occurring during PSS include down-regulation and transient desensitization of receptors. They reflect regulatory mechanisms which probably lead to destabilization of the serotonergic system during prolonged PSS (Flugge, 1995).

Gamma amino butyric acid (GABA), an inhibitory neurotransmitter (discovered in year 1950) is related to the amino acid, glutamic acid, a nutrient known to improve sleep. GABA reduces stress and helps the brain prepare for better sleep by activating brain receptors and calming nerves. It is produced in CNS and functions as a calming neurotransmitter in brain by inhibiting the nerve impulses related to stress and anxiety. When, the brain runs out of GABA, the signals between the nerves slow-down under stress. Symptoms of a GABA deficiency include anxiety, low sex drive, headache, heart palpitations, and even seizures (Harvey et al., 2002).

Dopamine is a neurotransmitter with a vital role in several functions of the brain that are sleep, mood, motivation, behavior, reward, cognition, attention and voluntary movements. As a result, any type of stress can have a significant influence on the cerebral dopaminergic (DA) system. Physiologically, the body responds to stressful conditions by activating the DA system, which triggers the release of dopamine. It is a precursor to norepinephrine, which is a stress hormone synthesized from dopamine and released in the body's fight-or-flight response to a stressful event. Research in neuro psychopharmacology shows that psychologically stressful situations also increase the release of dopamine, and the significant psychosocial stressors (e.g., mother-infant relationship disruptions) can have long lasting effects. The release of dopamine is a coping mechanism for the body when impacted by stressful conditions; the levels will rise and fall with the addition or removal of stressors respectively. In response to additional stress, the production of dopamine is increased which can provoke certain behaviors such as hyperactivity which is due to the role of dopamine in the control of movement, understanding, emotional reactions and impulsiveness (Bourdelais and Kalivas, 1991; Kalivas and Stewart, 1991).

The Endocrine system

It consists of series of glands located throughout the body that regulate metabolic functioning. The glands that are most closely involved with the stress response are pituitary, thyroid and adrenal glands. The pituitary gland is called the master gland due the fact that it manufactures several important hormones, which then trigger hormone release in other organs. The thyroid gland increases the general metabolic rate. Perhaps the gland that has the most direct impact on stress response, however, is the adrenal gland (Khansari et al., 1990)

When an individual experiences stress, the brain triggers the secretion of a cascade of stress hormones regulated by the Hypothalamic pituitary adrenal (HPA) axis. One of those hormones is cortisol where atypical cortisol concentrations and patterns have been linked to various outcomes in brain including high levels of aggression, impaired memory and the degradation of the immune system. Recent clinical studies have linked increased levels of cortisol with suppression of immune system. It appears that cortisol metabolizes (degrades) white blood cells. As the number of white blood cells decreases, the efficiency of immune system decreases, setting the stage for illness and disease. It has also come to light that the increased level of cortisol can direct the excessive amount of cholesterol into the blood, thereby adding to associated artery plaque buildup leading to hypertension and coronary heart disease. The adrenal medulla normally releases 80% epipherine and 20% nonepipherine, however under the influences of stress, upto three hundred times the amount of epinepherine can be found in the blood compared to the amount in samples taken at rest (Naik et al., 2006).

The neural impulses received by the hypothalamus as potential threats create a chain of biochemical messages, which is like a line of falling dominos cascade through the endocrine system glands. Based on the half life of these hormones and the speed of there metabolic reactions vary in length from hour to week in some cases of stress. This chain of reactions is referred to as the prolonged effect of stress (Naik et al., 2006).

Increased secretions of cortisol in blood act primarily to ensure adequate supply of blood sugar for energy metabolism. However, when increasingly high levels of cortisol are observed due to chronic stress, the integrity of several physiological system is compromised.

The Immune system

There are several useful ways of dividing the elements of the immune response. For the purposes of understanding the relationship of psychosocial stressors to the immune system, it is useful to distinguish between natural and specific immunity. Natural immunity is an immune response that is characteristic not only of mammals but also lower order organisms such as sponges. Cells involved in natural immunity do not provide defense against any particular pathogen; rather, they are all-purpose cells that can attack a number of different pathogens and do so in a relatively short time frame (minutes to hours) when challenged. However, the specific immunity is characterized by greater specificity and less speed than the natural immune response (Dantzer and Kelley, 1989).

Stress Induced Disorders

There are number of disorders generated through stress and the common disorders are ulceration, depression and sexual deficiency.

Ulceration

Stress-induced gastric ulceration is one of the most common forms of peptic ulcer. Peptic ulcer represents a serious medical problem due to its high frequency among different socioeconomic classes and it may result in disability, work loss and high-cost medical care. A positive correlation between stress and ulcer has been reported clinically, as stress may alter factors that pertain to mucosal integrity, leading to exhausted mucosal defense mechanisms. Although the role of the CNS in motor, secretory and endocrine functions of the gastrointestinal tract has been well recognized however, the chemical messengers involved in these gastrointestinal functions are hardly clear. In particular, despite significant efforts made to provide a mechanistic understanding of stress induced ulceration remains fragmentary. The CNS has been demonstrated to be involved in the genesis of stress-induced gastric ulceration. Various neurotransmitters found to be involved including GABA and drugs acting at the GABA-benzodiazepine receptors are useful in the prevention of stress induced gastric ulcers. Increased gastric acid secretion is one of the possible causes of stress-induced gastric ulcers (Das et al., 1997).

Depression

Though the body has stress hormones to warn us to respond and guard the body in case of emergencies or attack, the human body is not intended to handle stress for prolong duration as too much stress leads to depression (Brown et al., 1978; Peterson et al., 1978).

Some of the symptoms of stress induced depression include fatigue, imagined and actual pain, sleeping disturbances, panic attacks and nightmares. It has been observed that stress hormones can destroy and slow the growth of nerve fibers in hippocampus that can cause depression as well as memory loss. More than hundred neuro chemicals are found in the human brain, where norepinephrine, 5-HT, dopamine, and Ach are the main focus of biomedical research. Among these four high-profile neurotransmitters, 5-HThas the most widespread impact on the normal brain functioning. Changes in the level of serotonin can quickly alter the mood and hence it is referred to as the body's natural mood-altering agent. In addition the reduced level of serotonin in the brain leads to depression (Nuritova and Frenguelli, 2012).

Sexual Deficiency

A sexual problem, or sexual dysfunction, refers to a problem during any phase of the sexual response cycle that prevents the individual or couple from experiencing satisfaction from the sexual activity. Recent research shows that stress boosts the level of stress hormones viz. glucocorticoids (eg. Cortisol) that inhibits the sex hormone [gonadotropin releasing hormone (GnRH)] which subsequently suppresses the sperm count, ovulation and sexual activity. It has also been proved that stress increases the brain levels of a reproductive hormone named gonadotropin-inhibitory hormone (GnIH). The common thread appears to be the glucocorticoid stress hormones, which not only suppresses the GnRH but also boost the suppressor, GnIH which causes reproductive dysfunction. In humans, chronic stress can lead to a drop in sex drive as well as a drop in fertility and erectile dysfunction (ED) is defined as the inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse (Homodelarche et al., 1991).

Regulators of stress induced ulceration, depression and sexual deficiency

The molecular mechanism of stress induced disorders is regulated by the expression of proteins localized on brain endothelial and the testicular cells. One such regulatory protein is Phosphorylated glycoprotein (Pgp) which regulates the stress induced depression, sexual deficiency and gastric ulcers. Pgp, an ATP-driven efflux transporter (170kDa) belongs to multidrug resistance 1 gene (MDR1) family which limits the penetration of various molecules including therapeutic agents. In addition, Pgp is perhaps the best known and studied efflux transporter that serves as a defensive mechanism against the wide spectrum of non-polar therapeutic drugs and xenobiotics in normal state. However, during stress and normal aging, the expression of Pgp has been reduced and more recently it has been observed that the expression of Pgp is suggested as a key player in the etiology of AD. The basic of AD is the over accumulation of neurotoxic β-amyloid peptide (Aβ), which normally effluxed out of brain through Pgp. The down regulation of expression of Pgp is considered as the basic cause of Aβ accumulation (Fetisova et al., 2010; Thomas, 2005).

Substantially, the Pgp is an important channel of amyloid-β (Aβ) clearance mechanism which consists of two important features that are, its affinity towards Aβ and the efflux of Aβ peptides. Affinity of Pgp towards Aβ was confirmed by *in-vitro* binding studies whereas the efflux of Aβ peptides was identified by the level of Aβ peptides after pharmacological blockade of Pgp. Genetic variants in the P-gp account for differences in the clinical efficacy of antidepressants, most likely by influencing their access to the brain (Kania et al., 2011).

It has been observed that antidepressant induced remission of depressive symptoms which is predicted by single nucleotide polymorphisms (SNPs) in the ATP-binding cassette, sub-family B1 (ABCB1) gene among those depressed patients who were treated with drugs that are the substrates of the ABCB1 encoded Pgp. In the human brain and testis, the Pgp is highly expressed at the luminal surface of capillary endothelial cells, thus protecting brain and testis from potentially toxic substances. Pgp knockout mice have been shown to accumulate more Pgp substrates (e.g. vinblastine, nelfinavir) within testicular tissues than wild-type controls. Pgp is also expressed in Leydig cells, testicular macrophages, and Sertoli cells (Brunner et al., 2004).

Thus, Pgp is likely to be involved in protection of somatic cells from xenobiotics within the testis and may also influence the microenvironment of the seminiferous tubules through transport of testicular steroids. Pgp present in the blood-testis barrier (BTB) prevents the penetration of xenobiotics, thus providing protection for the testis. Reduced Pgp expression in the testis may lead to enhanced testicular penetration of toxic substances, which lead to damage of the testis and infertility (Cordoncardo et al., 1989).

Additionally, the Pgp is expressed at high levels along the entire human intestinal canal. Previous studies have also reported that Pgp is down regulated in patients with ulcerative colitis (UC) and genetic variation in the gene encoding Pgp, appears to be associated with susceptibility to UC (Englund et al., 2007). Hence, Pgp plays an important role in regulating the stress induced depression, sexual deficiency and ulceration. Medicinal plants useful in the treatment of such stress induced disorders are *Mucuna pruriens* (*M. pruriens*) and *Hypericum perforatum* (*H. perforatum*).

Role of Lithium in regulation of efflux mechanism via Pgp upregulation

Lithium is the lightest of all metals had multiple biochemical and molecular effects on neurotransmitter receptor-mediated signaling, signal transduction cascades, hormonal and circadian regulation, ion transport and gene expression. These effects have been widely associated with the activation of neurotrophic pathways and neuroprotection (Chuang et al., 2002).

Apart from the involvement of lithium in upregulation of Pgp expression, the growing evidence suggests that lithium has neuroprotective effects against a variety of insults, including glutamate-induced excitotoxicity, ischemia-induced neuronal damage and other neurodegenerative conditions reduces the efflux action across the BBB (Lange et al., 1998).

In fact, recent research has recognized prominent molecular and cellular targets associated with lithium's neuroprotective effects. These include its ability to affect intracellular signaling pathways including activation of canonical Wnt signalling, and affect the transcriptional activity and gene expression to promote the Pgp mediated efflux capability of endothelial cells (Matsuoka et al., 1999).

Pharmacological effect of lithium chloride (LiCl) on expression of Pgp in stressed animals

LiCl, a well knownneuroprotective agent which tends to maintain plasticity of neurons. It has been observed that LiClupregulates the expression of Pgp via activation of Wnt/β-catenin signalling. With a potential inhibitory action on glycogen synthase kinase 3β (Gsk-3β), a key inhibitory protein of Wnt pathway. The attenuation of Wnt/β-catenin signaling has been recently shown to be mediated by a direct binding of neurotoxic Aβ peptides to the Wnt protein via activation of Gsk-3β which inhibits the level of β-catenin (a key transcription factor of Wnt/β-catenin pathway) in the cell.()It is observed that lithium inactivates the GSK-3β, and acts as a positive regulator of the Wnt/β-catenin signalling pathway and prevents the cytotoxic effects and metabolic impairments of neurons by Aβ fibrils (Zaragosi et al., 2008; Orena et al., 2000) However, LiCl prevents the neuronal degeneration in rats and averts the behavioral impairments induced by Aβ fibrils. Though, lithium mimics the Wnt/β-catenin signalling by inhibiting Gsk-3β, promoted the survival of post mitotic neurons against Aβ neurotoxicity and stabilized the level of β-catenin (Daniel and Reynolds, 1999) which may enhance the expression of P-gp and improve the functioning of BBB and BTB during stress.

The role of Wnt/β-catenin signalling in regulation of Pgp

Based on the previous neuroprotective data and the effect of Wnt agonists and Gsk-3β inhibitors, it has been observed that LiCl enhances the expression of Pgp in human brain endothelial cells (hCMEC/D3) following an activation of Wnt/β-catenin signalling pathway. The increase in protein and gene expression of Pgp after LiCl exposure to hCMEC/D3 cells indicates the functional significance of Wnt/β-catenin pathway in regulation of efflux mechanism across the BBB. Though the efflux transport system consist efflux transporters (Lrp-1 and Pgp) at the abluminal and luminal surface of endothelial cells respectively which efflux xenobiotics into the blood stream. Apart from the regulation of Pgp expression, it has been reported that the Wnt/β-catenin signalling is a key regulator of efflux mechanism in endothelial cells which might follow the similar mechanism in testicular cells (Chen et al., 2013; Jacques et al., 2012; Kolben et al., 2012; Lu et al., 2012).

Role of medicinal plants in regulation of stress

In the ancient Indian Ayurvedic and Unani medicine systems, numerous plants and their products have been recommended for endurance against stress and its induced disorders. Medicinal herb and plant extracts are considered as effective medicines to be respected and are appreciated for its major role in "modern pharmacy". There has been an explosion of scientific information concerning plants, their crude extracts, and their derived substances during last 2-3 decades. Although herbal medicine has existed since the dawn of time, but the exact mechanism through which phytoconstituents produces a therapeutic effect remains largely unexplored. Number of plants are claimed to possess an anti-stress potential (Ghosal and Bhattach, 1971; Greeson et al., 2001).

Table 2 List of reported plants as anti-stress

Common name	Botanical name	Uses
Korean Ginseng root	*Panax ginseng*	Antioxidant, antiinflammatory, amphoteric antiasthmatic, cardiotonic, CNS stimulant
American Ginseng	*Panax quinquefolius*	Antioxidant, antiinflammatory, bitter tonic, immune amphoteric
Eleuthero	*Eleutherococcus senticosis*	Anticholesteremic, antioxidant, nervine. antiinflammatory (mild), immune potentiator
Berries	*Schisandra chinensis, S. splenathera*	Antioxidant, antiinflammatory, astringent, antiasthmatic,hepatoprotective, amphoteric
Ashwagandha	*Withania somnifera*	Antiinflammatory, antioxidant, antispasmodic, astringent, immune amphoteric, sedative
Shatavari	*Asparagus racemosus*	Anti oxytocic,antiepileptic, antiulcer, antiimflammatory, antipyretic, analgesic
Dang Shen	*Codonopsis pilosula*	Gastroprotective, hypoglycemic agent, immune potentiator, nervine
Licorice	*Glycyrrhiza glabra, G. uralensis*	Antihistamine, antiinflammatory, antidiuretic, antioxidant,antitussive, antiviral, demulcent, hepatoprotective, immune amphoteric, gastroprotective
Cordyceps fungus	*Cordyceps sinensis*	Antiasthmatic, antileukemic, antioxidant, hepatoprotective, immune potentiator, nephroprotective, sedative
Tulsi	*Ocimum sanctum*	Antibacterial, anticholesteremic, antidepressant, antioxidant, antiviral, carminative, expectorant, immune amphoteric
Rhodiola	*Rhodiola rosea, R. crenulata*	Antiinflammatory, antioxidant, antidepressant, cardioprotective, immune potentiator

Summary and conclusions

Although, stress has long, been the object of study, but we are only beginning to understand its complexities. Through novel techniques, it is also possible to measure the response of the primary stress systems in a convenient, non-invasive manner. Thus, allowing the research to progress rapidly in the area of stress which is important to improve quality of life. By gaining a thorough understanding of the systems governing stress response, the intervention techniques can be developed to target the over-activation of these systems, decrease stress, and improve health. The recent findings concerning stress induced disorders are a solid starting point for much needed future research.

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Conflict of interest

Authors did not have any conflict of interest.

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