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Stress: A Key Player for the Induction of Many Diseases

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Abstract

Background: The life of 21st century individuals is full of stress. Different factors leading to stress are stressors. Stressor may have both negative and positive effects on personality and health as well. Chronic exposure to the stress elicits a number of disturbances in hormonal and nervous functioning leading to major health complications.

Mechanism: The two main mechanisms underlying health complications due to stress are sympathetic-adrenal-medullary (SAM) axes and hypothalamic-pituitary-adrenocortical (HPA). Cortisol is the main hormone of HPA axis whose disturbed levels are involved on the basis of diseases due to stress. HPA activation controls, anti-inflammatory processes, metabolism of fats, carbohydrates, proteins and gluconeogenesis by cortisol. In a similar way, catecholamine released as a result of SAM activation regulate a number of functions like cardiovascular, pulmonary, hepatic, skeletal muscles and immune system in collaboration with autonomic nervous system. In GIT, stress causes an imbalance of bicarbonates and acid secretion, mucosal layer get disrupted, leading to gastritis and ulcer.

Effects: Ability of the body to fight against different diseases decreases, leading to serious health problems like cancer. Stress not only affect to the person suffering from different environmental stressors but it may also have deleterious effects on fetus if pregnant female is under stress. Chronic stressors may also cause serious mental disorders like depression.

Conclusion: Stress is a main factor leading to DNA alternations leading to early aging and death. This study describes the severity of stress and stressors by describing the underlying mechanisms that get disturbed and leads to serious health issues and even death.

Keywords: Stressors; hypothalamic-pituitary-adrenocortical (HPA) axis; Sympathetic-adrenal-medullary (SAM) axis; Health complications

1. Introduction

Stress is a psychological process which occurs when individual's environmental demand exceeds his or her adaptive capacity. Stress may have both negative and positive effects on individual personality and health. When an individual tolerates stress and take it to enhance his abilities and performance, stress is positive and called as eustress. When the ability of individuals to manage with environmental measures decreases, it may lead to event elicited negative effects and called as distress. The environmental events causing stress are called as stressors. Stressors may be acute (lasting for minutes), brief (for smaller duration) or chronic (long lasting) [1]. Individuals of 21st century are facing a wide array of stressors, especially in developing countries like Pakistan. Common life stressors include death, divorce, grievance, personal fight, taking care of a sick family member and business problems. In Pakistan like countries, unemployment is very serious and important stressor. Work related stressors may include starting a new job, insecurity about advancement or risk of termination, facing discrimination or harassment, working in dangerous conditions, working long hours, being unhappy with the job, hectic routine and to give a speech in front of colleagues. Here in this discussion, stress does not include psychiatric disorders that may cause stressful behaviour. Negative effects, e.g., feelings of anxiety and depression play vital role in pathogenesis of the physical diseases that may influence the normal biological processes and behavioural pattern ultimately leading to increased disease risk. Chronic stress causes eternal variations in physiological, emotional and behavioural reactions and play most toxic role in susceptibility and occurrence of disease [2].

2. Psychological Stress Related Diseases

Significant relationship has been established between daily stress and incidence of both contemporaneous and consequent health problems like influenza, sore throat, headaches and backaches. Frightening is the mortality and morbidity case due to stress related sickness. Emotional stress is the one of the six central causes of death in developing countries [3]. Stress may subsequently lead to more complex health issues like cancer, acquired immune deficiency syndrome (AIDS) and autoimmune diseases [4], gastrointestinal diseases, sleep problems, depression, respiratory disorders, cardiovascular diseases and suicide [5]. Psychological stress may also affect fetal development during pregnancy [6]. However cascade of the events happening at different stages of life, environmental factors and genetic predisposition collectively defines the susceptibility to stress leading to different diseases as illustrated in Figure 1. An incident causing disease in one person may not affect the other. It depends upon the individual way of coping with the situation that differentiates the susceptibility of stress and related diseases. The perilous aspect related to stress and ultimate effects on health is its long-lasting outcome. Whenever individual's environment becomes unusual, sympathetic fight or flight system of the body got activated. Under normal circumstances, within three minutes of removal of unusual condition, fight or flight responses subside, body get relaxed and return to its normal condition. Chronic stressors majorly due to restrained annoyance that we embrace in our self instead of discharging, especially when their effects become cumulative, influence almost every system in the body. As a result

of chronic stress, when sympathetic discharge of adrenaline declines, corticosteroid secretion continues as above normal levels. If stress continues and the body is unable to adapt the situation, there is likely to be broken down of bodily resources.

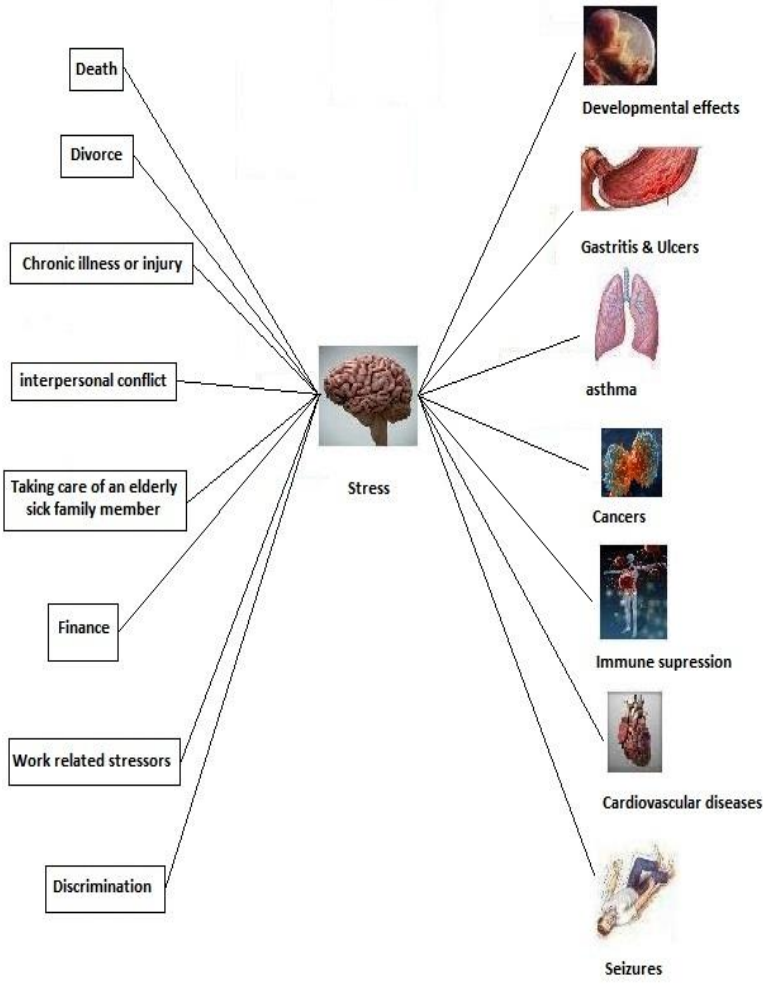

Figure 1: Life stressors lead to many health complications.

Stress causes activation of endocrine processes that provides a key pathway for further effects on health. Two main endocrine systems are involved: hypothalamic-pituitary-adrenocortical (HPA) and sympathetic-adrenal-medullary (SAM) axes. Cortisol is the main culprit controlling a number of physiological processes due to HPA activation like anti-inflammatory processes, metabolism of fats, carbohydrates, proteins and gluconeogenesis. In a similar way, catecholamine released as a result of SAM activation regulate a number of functions like cardiovascular, pulmonary, hepatic, skeletal muscles and immune system in collaboration with autonomic nervous system. Exposure to stressors causes activation of these endocrine systems. Prolong activation of HPA and SAM causes an impaired control on physiological systems responsible for physical and psychiatric illness as shown in Figure 2.

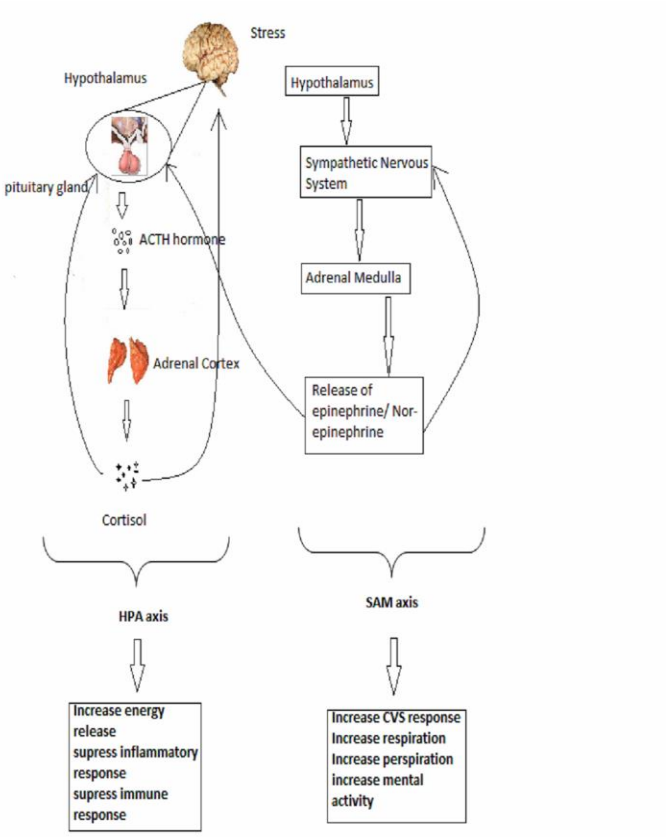

Figure 2: Mechanisms involved in health complications due to stress.

3. Effects of Stress on Immune Responses

The immune system is the key way through which stress translates itself into physiological changes. Depending upon the principle cellular and molecular components, immune system responses are categorized into immunoprotective, immunopathological and immunoregulatory responses. Immunoprotective responses are involved in wound healing, viral infection and cancer elimination. It is also responsible for vaccine induced immunological processes of immune system. Immunoprotective responses are rapid and efficient in clearance of activating pathogen with a rapid resolution of inflammation. Innate and adaptive type-1 and type-2 immune systems may be involved in immunoprotection. Immunopathological responses are the basis of autoimmune diseases in which autoantibodies are produced. The response may be chronic and non-resolving inflammation. Low level long term elevation in local or systemic inflammatory mediators may also involve immunopathology that are responsible for illnesses like cardiovascular disease, depression and obesity. Immunoregulatory responses involve immune cells and factors that are responsible for other immune cell inhibition. They are also called as inhibitory responses. Immunoregulatory responses keep a check upon proinflammatory, allergic and autoimmune responses. Some studies suggest that immunoregulatory factors suppress antitumor immunity leading to various types of cancer.

Immunologic mechanisms may permit stress to "get inside the body" and aggravate indications of different illnesses. It depends upon different factors that cause the stress to affect immune responses. Stressor may enhance or suppress immune functions, as shown in figure 2, the end effect of which is responsible for effects on health of an individual. The end effect may be positive or negative. Suppression of immunoprotective responses due to stress may be harmful for health while stress induced exaggeration of the immunopathological responses has harmful effects on health as shown in Figure 3. Stress induced enhancement of immunoregulatory responses may be useful in case of autoimmune and proinflammatory ailments and may have damaging effect on cancers [7].

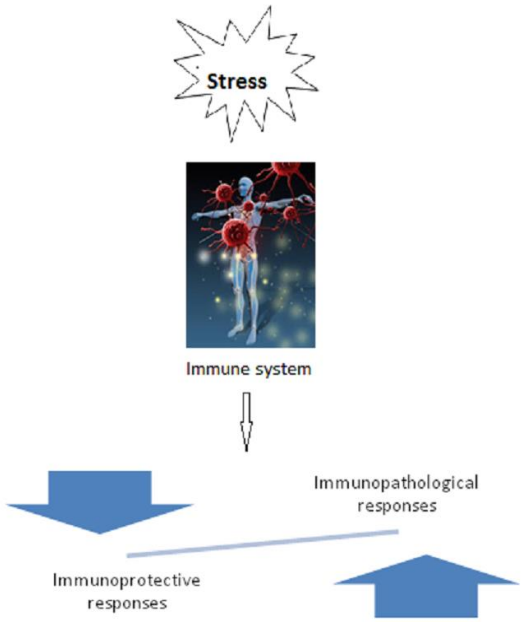

Figure 3: Immbalance between immunoprotective and immunopathological responses leads to defective immune system.

Immune responses are carried about through immune cells. Stress causes changes in population of these immune cells. Increased level of corticosterone induced by stress causes a prominent decrease in the number and percentage of lymphocytes. It also increases the number and percentage of neutrophils. Stress causes greater decrease in B cell, NK cell and monocytes levels than T cells. Leukocytes number changes depend upon the time of exposure of stressors which are rapidly reversed after cessation of stress. Endocrine factors activated during stress cause change in immune cells in blood and other immune compartments. These changes lead to the altered immune ability to cope up with stress and to respond to potential immune challenges [8].

4. Stress and Gastrointestinal Diseases

Gastritis caused by stress is known as a stress ulcer syndrome and it can cause haemorrhages in critically ill patients under life threatening physiologic stress, which can lead to mild to severe gastrointestinal bleeding if not treated. The mucous layer under the stimulus of prostaglandin forms a barrier between vagal nerve stimulation and acidic pH of the stomach. This protective barrier is demolished in the presence of toxic agents and acid turgid back to the epithelium causing mucosal damage. Blood flow to mucosa decreases of stress, which can lead to ischemia that destroys the mucosal lining. Blood flow to GIT reduces more if the damage is severe thus it cause additional compromise of the mucosal barrier and increase the risk of gastritis.

A Study in rats illustrated that minor restraint stress energized the inflammatory procedure in rats recuperated by TNB colitis 6 weeks. It was imitated without convoying structural destruction by the proliferation of colonic myeloperoxidase action. Though a following study in totally improved mice from hapten-induced colitis 8 weeks illustrated that explicit inflammation with mucosal ulceration and a polymorphonuclear leukocyte infiltration takes place by a mishmash of mild restraint plus acoustic stress with a sub threshold dose of the hapten supplied intra-rectally. The stress-induced reactivation of colitis is transported from spleen and mesenteric lymph nodes by a CD4 augmented population of lymphocytes as shown in Figure 4. Reactivation of colitis occurs with an increase in colonic permeability and stress reduces the mucous secretion. Reactivation of colitis occurs when stress couple with sub threshold intra-rectal dose of hapten that require the presence of CD4+ cells. The offered mechanism for reactivation of colitis is an increase in permeability and stress induced decrease in mucin [9].

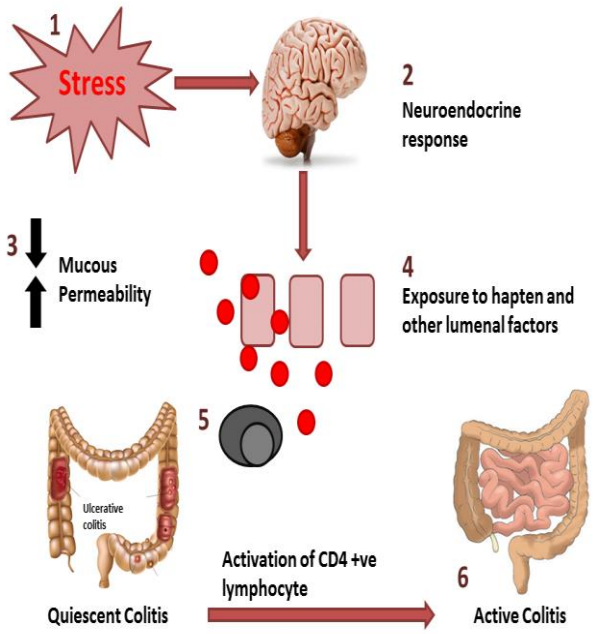

Figure 4: Mechanism underlying stress-induced reactivation of colitis.

4.1 Stress and heart diseases

Stress is a threat for other heart diseases, though high levels of stress may worsen other factors like high cholesterol and high blood pressure. The incidence of heart complications due to stress is given in percentage in Figure 5. Stress can turn into heart diseases in two ways;

- Coronary artery disease, stroke and peripheral artery disease is caused by chronic emotional stress which can lead to atherosclerosis.
- Intense stress can cause acute heart problems such as heart attacks.

People re-join in different ways to other circumstances like for one person if the event is jubilant and enjoyable, but for another person the same event may be despondent and infuriating. Some people handle life challenges with affluence, but other people worsen the situation by their annoyance, culpability, nervousness and sullenness. Deep abdominal fat deposition occurs due to stress, which secretes inflammatory cytokines and causes insulin and metabolic syndrome. Level of homocytoseine, fibrinogen and CRP may also increase leads to coronary disease. Blood flow to the heart is reduced by acute stress that encourages the irregular heart beat and probability of blood clotting. These damaging effects affect the lining of blood vessels which makes them more atherosclerotic [10].

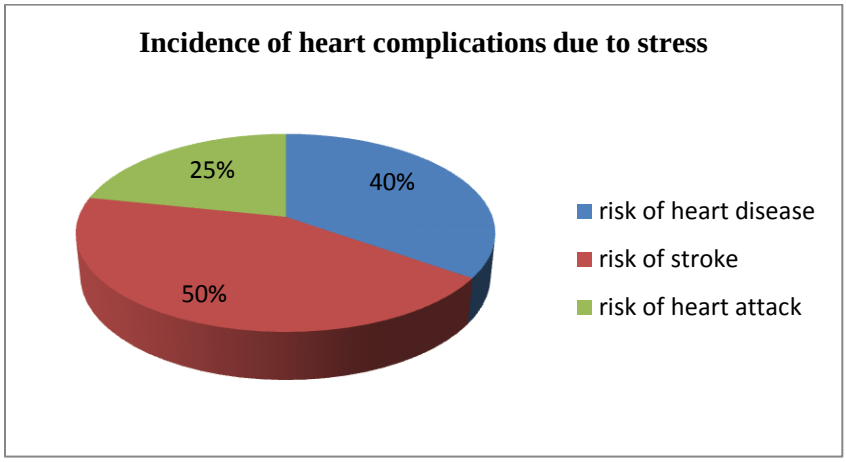

Figure 5: Percentage incidence of heart complications due to stress.

4.2 Stress and Atherosclerosis

People are at extreme stress exhibiting thwarting, annoyance and aggression reacting to emotional stress. Everyday life stress worsens the vascular function temporarily by hormonal changes and increase of adrenaline in the bloodstream. High risk of atherosclerosis is caused by increased inflammation due to chronic stress. Angiography illustrates a substantial increase in coronary atherosclerosis when the patient's cholesterol level decreased by 60 mg/dl (Shub et al., 1981). Cardiovascular risk factors increase the risk of chronic emotional stress. Increase consumption of tobacco is more common in smokers under stress and weight gain is common in people under emotional stress which in turn increase the cholesterol level. Atherosclerosis is accelerated by two ways

- Cardiac risk profile worsening
- Directly affecting the blood vessels

4.3 Stress and acute heart conditions

Quick cardiac death and acute coronary syndrome are caused by severe emotional stress. Other risk factors of acute coronary syndrome are stressful life events like death of loved one, failure in business, unemployed, serious family conflicts, being violence victim and exposure to disasters. The substantial increase in blood pressure, vascular tone, constriction of the veins, inflammation, heart rate, blood clotting are the risk factors that lead to acute cardiac risk. Stress is also responsible for other cardiac conditions like broken heart syndrome or stress cardiomyopathy [10].

4.4 Stress induced cancer

The substantiation that stress cause cancer is frail. The relation could arise in numerous means between psychological stress and cancer. Individuals suffering from stress may adopt specific health related activities like smoking, overeating and intake of alcohol that enhances their risk of developing cancer. Sometimes cancer is inherited.

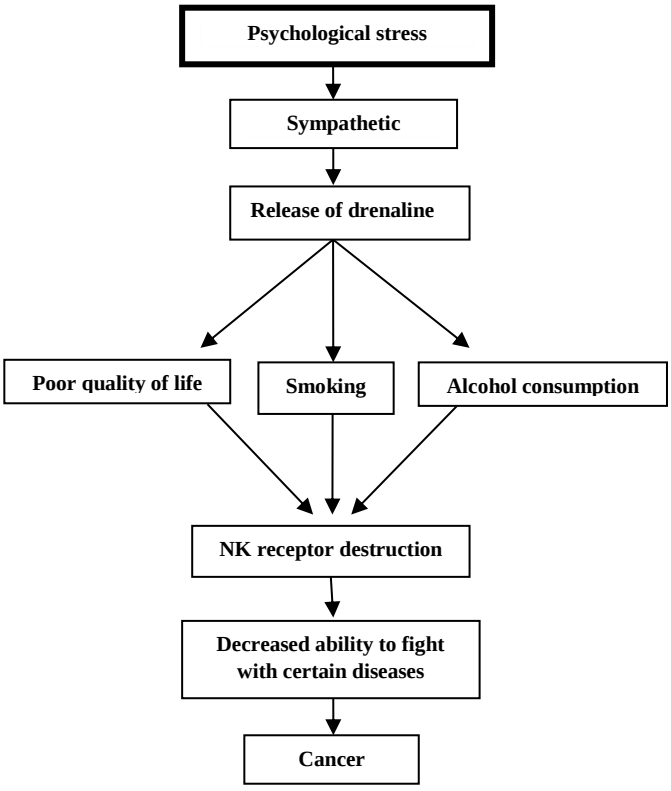

Figure 6: Possible mechanism of cancer due to stress.

In 200 AD, Galen proposed that melancholic women were more susceptible to cancer than women who were sanguine. Epidemiologic studies have shown that psychological and social characteristics might be associated with differential cancer progression, incidence and mortality. The cancer survival individuals managing their stress by their specific habits like smoking and intake of alcohol may have pitiable life after treatment of cancer, which may be the possible mechanism of cancer due to stress as shown in Figure 6. On the other hand, the individuals having fruitful approaches to manage their stress like complete mental and physical relaxation have less anxiety level. Psychological stress aggravates the ability of tumour growth and metastasis [11]. Recent studies in mice bearing human tumours show that tumour growth, increase and it metastasize under stressed conditions. Experiments on mice transplanted with tumour into their mammary fat showed increase metastasis to the lungs and lymph nodes under chronically stressed conditions. Different laboratory studies in human cancer cells and mice found that norepinephrine, which is a stress hormone may stimulate metastasis. Though there is no substantiation that cancer is directly developed from stress. A latest study found a relation between tumour, stress and natural killer cells. The natural killer cells have a strong association to abolish metastasis and to fight against diseases. Though the consequence is not ultimately that shows the stress destroy the activity of natural killer cells. The other introductory study disclosed the high level of stress in breast cancer patients with proof of enfeebled immune system [12].

4.5 Asthma Due to Stress

The increased stress exposure is associated with increased respiratory illness susceptibility. Chronic stressors are more involved in such effects rather than acute ones. Stress may either lead to respiratory illness by activation of hypothalamic-pituitary-adrenocortical (HPA) and sympathetic-adrenal-medullary (SAM) axes or by stimulation of two main disunions of sympathetic, parasympathetic and autonomic nervous system. Stress is involved in the alternation of inflammatory responses in airways brought about by allergens, irritants and infections in people with asthma. On acquaintance to acute stress, sympathetic-adrenal-medullary (SAM) hypothalamic-pituitary-adrenocortical (HPA) got activated. This activation causes an increase in the secretion of cortisol, epinephrine and norepinephrine. After long exposure to these stress hormones, their receptors are down regulated. As a result, inflammatory responses to asthma triggers are modulated leading to increased Th2 cytokines production and eosinophils conscription. Both of these factors are considered to be the part of life stressors in asthmatic patients. One study showed that the asthmatic patients and healthy individuals have the same baseline IL-5 a production with there is no stress. After exposure to stress, IL-5 level in asthmatic patients was greater than healthy individuals and hence excessive responsiveness to asthma mitogens. Another study showed that both healthy and asthmatic patients have reduced Th-1 cytokines IFN-g and IL-2 but production of pro-inflammatory cytokines IL-6 level was raised. Excessive amount of IL-6 was produced in nasal cavity ensuing immunization and more sever exaggerated symptoms. These findings can explain the cytokines serving as the primary mediator linking stress and disease.

Some stressors are considered to be triggers of HPA axis. ACTH and cortisol levels are increased in humans due to stress exposure [13]. Due to down regulation of expression, prolong cortisol exposure and functions of cortisol receptors occurs, leading to decreased sensitivity of immune cells to glucocorticoid and enhancing resistance.

Asthma in children leads to chronic and acute stress displayed 5.5 fold reduction in glucocorticoid receptor mRNA. The bioavailability of GR in leukocyte decreases in asthmatic children.

Stressors also have effects on sympathetic system. Fight or flight condition, systemic release of epinephrine occurs from adrenal medulla and activation of noradrenergic fibres innervating pulmonary and lymphoid tissues. The sympathetic discharge causes bronchodilation through endothelial smooth muscles and submucosal glands. Spleen, thymus and lymph nodes release catecholamine's that bind to lymphocytes and exaggerate hormonal responses. T-cells and B-cells possess adrenergic receptors regulating various features of humoral responses involved in asthma. These responses include IL-4, 5, and 13 expressions due to allergens, histamine release from activated mast cells and eosinophil recruitment and activation in airways. Prolong exposure to high levels of catecholamine's cause receptors down regulation in pulmonary and lymphoid tissues, leading to the bronchodilator effects of beta agonist therapies in asthmatic patients, exaggerated Th-2 cytokines expression, mast cell degranulation and eosinophil activation. Figure 7 shows different events consequently leading towards asthma and its exaggeration [14]. Parasympathetic nerve fibres innervates from vagus nerve smooth muscles and submucosal glands in the airways. Due to parasympathetic activation, acetylcholine is released, causing bronchoconstriction and mucus secretion. Stress causes hyper responsiveness of both alpha-sympathetic and parasympathetic pathways.

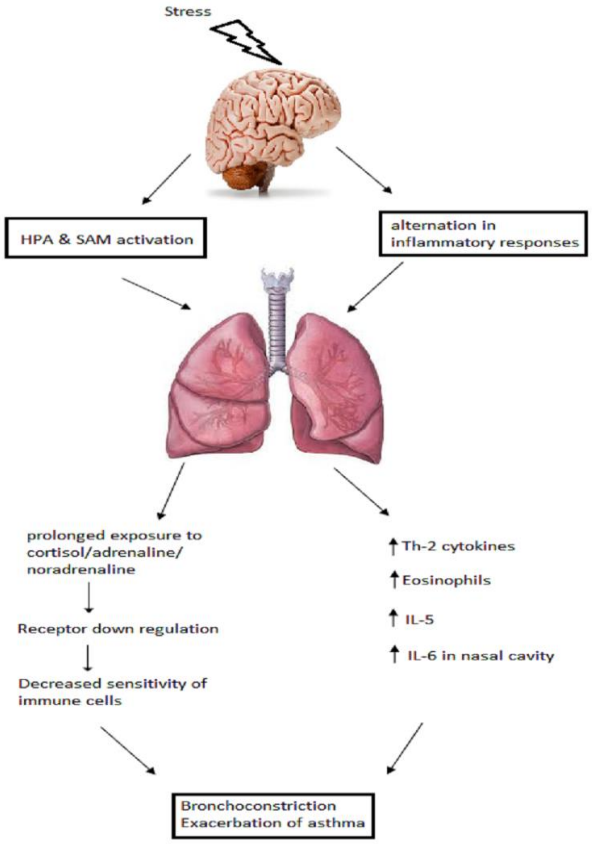

Figure 7: Processes involved in exacerbation of asthma due to stress.

4.6 Effect of Stress on Fetus

Most women experience stress while pregnancy. Neurodevelopment takes place during the prenatal period. At this stage fetus is vulnerable to the conditions and factors that may effect on brain development, behaviour and physical health. Common life stressors exposure to pregnant female may lead to abnormalities in fetal neurodevelopment including increased risk for mixed headedness, autism, affective disorder and decreased cognitive ability [15]. Stress exerts its negative effects not only during pregnancy, but it also has its long lasting effects even after birth. Stress exposure during pregnancy may be responsible for different mental illness at different stages of childbirth. Women's psychological distress causes physiological alternation which ultimately affects fetal health. As pregnant woman's nutritional influences fetal health, similarly women's distress has a long term effect on fetal health. Distress during pregnancy may alter the fetal heart rate, fetal activity, sleep pattern and movement. These alterations may have a possible mechanism of 'maternal-fetal HPA axis' and 'intrauterine environmental disruption due to uterine artery flow'. Woman's mental health is very critical for proper child growth during pregnancy. There is a lot of other pregnancy associated conditions like gestational diabetes, which are monitored regularly but mental condition is not considered usual. It is very critical to regularly evaluate woman's psychological state for the long term good health of new born [16]. Otherwise, not only the mother, but fetus also suffers a number of prenatal and postnatal complications as described in Figure 8.

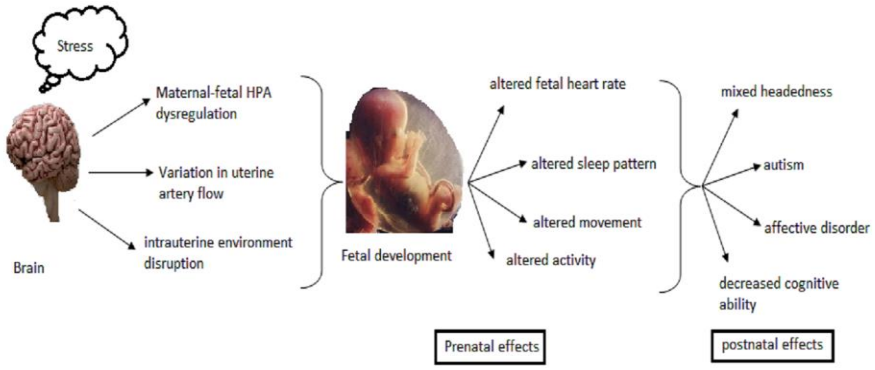

Figure 8: Prenatal and postnatal effects of stress on foetus health.

4.7 Stress induced diabetes mellitus type II

Diabetes mellitus is highly prevailing metabolic health complication that has also been linked with stress and psychological factors. Chronic stressors and stress hormones may lead to type II diabetes mellitus however, it may also precipitate type I in some genetically susceptible patients. The main mechanisms involved in stress induced health complications are considered to be involved in abnormal glucose release and metabolism also i.e. HPA-axis and SAM-axis activation [17]. Pathophysiology underlying stress induced diabetes mellitus is seemed to involve

abnormal sympathetic outflow. Sympathetic arousal causes excessive hepatic glucose output which cannot be properly metabolized due to the unequal insulin presence.

Some studies have discussed that exposure to chronic stressors initiates a chain of inflammatory processes involving major stress hormones as mediators like epinephrine, norepinephrine and cortisol. Free fatty acids produced as a result of lipolysis and proinflammatory cytokines also act as major inflammatory mediators of inflammation in visceral fats and vasculature. Epinephrine and norepinephrine activate NF_kB in macrophages, visceral fats and endothelial cells, leading to inflammatory responses cascade involving acute phase response of the innate inflammatory system. These inflammatory responses are considered to be involved in metabolic abnormalities leading to insulin resistance, a major risk factor for NIDDM [18]. Figure 9 describes the stress elicited events disturbing metabolic mechanisms and causing diabetes.

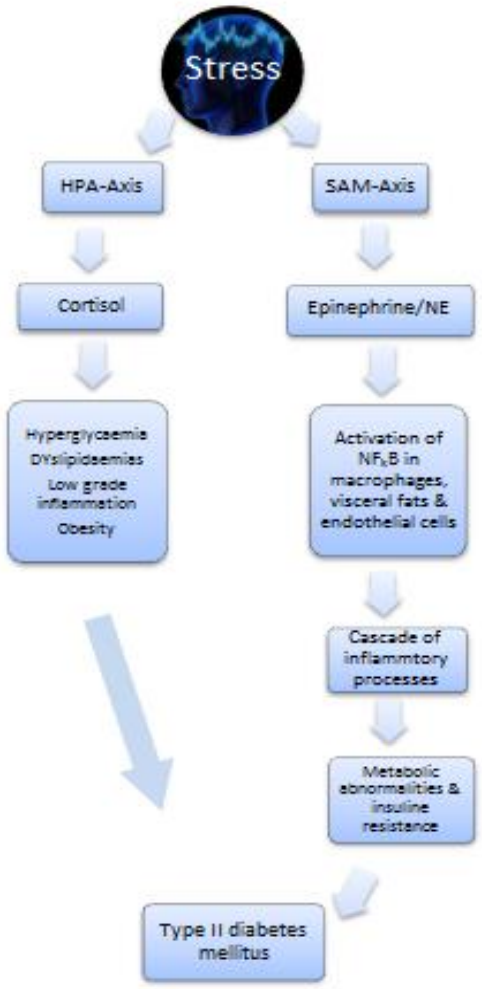

Figure 9: Stress induced metabolic disorders.

5. Depression

Depression is a drastic, potentially fatal, and extensive psychiatric illness, having a prevalence of approximately 340 million cases universally. Depression is anticipated to exemplify the primary reason of illness, universal by the year 2030. Depression is a major risk factor for metabolic diseases, cardiovascular diseases and suicide. Increase in depressive symptoms is caused by stressful life events and beginning of depression in adults and teenagers. The study shows that the development of depression, changes the role of stress. Studies focus on infantile is treated special and negligence has also described a connotation with risk for depression. Individuals are more likely to develop depression in their lifetime that experienced childhood abuse. An individual experiencing early childhood abuse has earlier onset, acute symptoms, longer duration, and depression [20, 21].

5.1 The Stress-Depression Connection

Chronic stress increases the level of stress hormones like cortisol and decrease the level of serotonin and other neurotransmitter in the brain that includes the dopamine. On normal working they control the biological processes like mood swings, sentiments, craving and sleep. When the stress response return or fail to shut off then it can lead to depression in vulnerable people. Immune and inflammatory system abnormality in depressed and suicidal patients has also been observed. The similar changes have also been observed by others. Cytokines level increases in depression patients, which can increase the level of stress hormones like corticotrophin releasing hormone (CRH), cortisol and adrenocorticotrophic hormone (ACTH) and may precipitate to HPA dysfunction [22, 23].

Stress increases levels of glucocorticoids by altering the CRH-ACTH signals. The release of glucocorticoids and pro inflammatory cytokines (IL-1β, IL-6, CRP, TNF-α, INF-α) is induced by stress which in turn increase the levels of glucocorticoids that acts on the brain by varying the CRH-ACTH signalling as illustrated in Figure 10. The red arrows show the suppressive effect while green arrows are showing stimulating effect. Neurologic and psychiatric diseases are associated by degranulation of microglia that leads to critical changes in neuronal activity [24, 25].

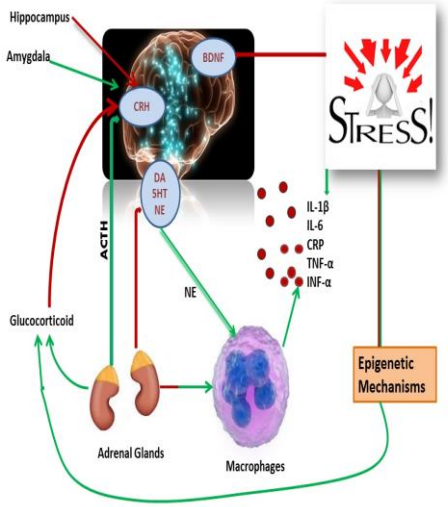

Figure 10: Schematic representation of direct and indirect effect of stress on inflammation and neuroplasty related processes.

6. Obesity

Stress is associated to biological variations that activate hunger and lead to obesity. The stealthiest aspect about the connection between stress and obesity is that it inclines to be self-reinforcing Bonnie Taub-Dix, RD. Taub-Dix says if that causes them to gain weight that can cause even more stress. The modern way of life in industrialized societies is characterized by increased intake of processed food, sedentary lifestyle and increased psychological stress, forming an environment that differs completely from that of our predecessors, which has driven human evolution until recently. Thus, it is not surprising that the rates of obesity and stress-related complications have been exponentially with the increase over the past decades. Recent data indicate a strong interplay between stress and obesity, which directly affects the activity of the hypothalamic-pituitary gonadal (HPG) axis. Specific hormones may play a role in this process.

6.1 Serotonin

The fattening comfort food during stressful times is an attempt to self-medicate. Eating carbohydrates raises the body's serotonin level," Taub-Dix says. “Serotonin is the body's feel-good chemical. It makes you feel well. "Very often the carbohydrates that people go form are laden with fat, like muffins, pastries, doughnuts, and cookies," Taub-Dix observes. "It's not like they're going for whole-wheat pasta."

6.2 Cortisol

Cortisol is a hormone which manages the fat storage and energy use in the human body. It also maintains the homeostasis and increase craving for fatty and sugary food. Excess cortisol is released from the body in case of chronic stress.

6.3 Neuropeptide Y

Neuropeptide Y raises the fat accumulation in the body and is released during stress from nerve cells. Stimulation of neuropeptide Y increases by high sugar and fat consumption. In the previous years in USA the extensiveness of obesity has increased intensity. Upper body obesity is related to the type 2 diabetes, hypertension and dyslipidaemia. The clustering of symptoms with insulin is described by these connotations. The hypothalamic pituitary adrenal is a stress related neuroendocrine system. The paraventricular nucleus (PVN) of the hypothalamus cause the secretion of corticotrophin releasing hormone (CRH) that encourage the synthesis of adrenocorticotrophic (ACTH) from the anterior pituitary gland [26]. PVN neurons are activated by physical stressor like haemorrhage and hypoglycaemia by expressing arginine CRH and vasopressin.

The clinical observation on Cushing’s syndrome is the basis that cortisol level is influenced by obesity and metabolic disease. In Cushing’s syndrome patient’s obesity is reversed by the adrenalectomy. The production of other inflammatory mediators and cytokines is stimulated by the cortisol. A current study stated that a higher BMI was related to decreased anti-inflammatory action of glucocorticoid [27]. The combination of decreasing lean body

mass and accumulation of trunk and abdominal fat is similar to Cushing's syndrome. It is often called as pseudo-Cushing's state. In the present society, chronic stress is an innovative risk factor for metabolic syndrome [28].

The common relation between visceral obesity and chronic stress is the prime clinical connection of metabolic syndrome as shown in Figure 11. The IL-6 and TNF-α overproduction occur by intensifying adipose tissue that additionally encourages the HPA axis accordingly making a vicious cycle. The stimulatory effects are characterized by solid lines and inhibitory effects by dashed lines. The appetite and energy disbursement is controlled by the central components of the stress system, which is most likely to CNS Centre [29]. The consumption of carbohydrate and less energy disbursement by subduing CRH is promoted by successive rise of glucocorticoid concentration [30]. The glucocorticoid under chronic stress helps the consumption of edibles which leads to visceral obesity.

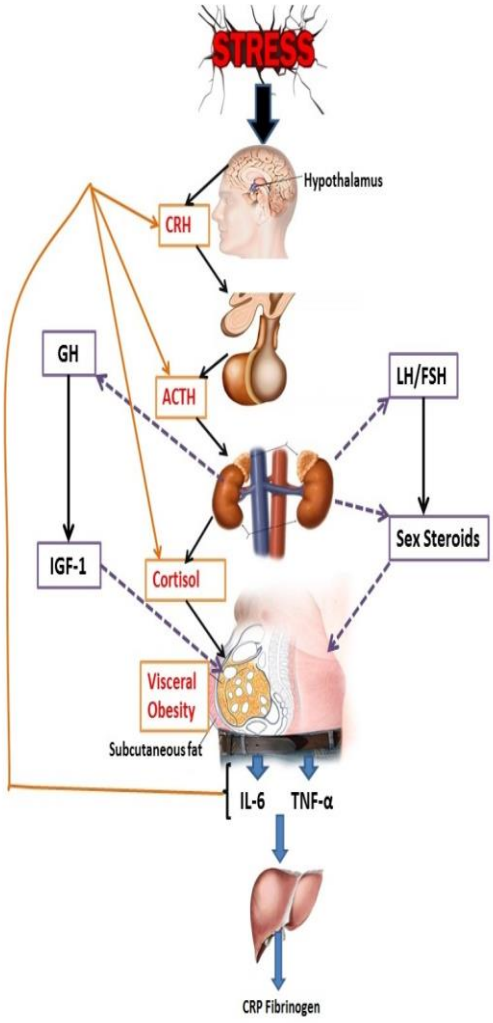

Figure 11: Stress induced metabolic disorders and obesity, CHR: corticotropin-releasing hormone, ACTH: adrenocorticotropic hormone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, GH: growth hormone, IGF-1: insulin- like growth factor-1, TNF-α: tumor necrosis factor-α, IL- 6: interleukin-6, CRP: C-reactive protein.

7. Stress Induced Cellular Aging

Chronic diseases are a major reason of cellular aging. One of the important factor that appears to be the cause of early onset of age related diseases in chronic psychological stress. Stress causes anabolic/ catabolic imbalance. It may also lead to biochemical imbalance. Cortisol, glucose and insulin levels are raised due to chronic stress while androgens and growth hormone levels are decreased. This imbalance initiates the oxidative stress and systemic inflammation leading to cell aging process abnormalities. As we have discussed that stress is a major factor causing metabolic disorders, obesity and insulin resistance. Obesity also plays a key role in the cell aging process. Biochemical imbalance leads to leukocyte aging directly by cortisol effects and indirectly by adiposity.

Whenever the body is exposed to some harsh environment or stressor, it always tries to adapt or compensate these changes in order to protect the genome. In case of chronic stressor, the set point of certain regulatory system and responses are altered. These altered set points are main reasons of cellular aging. Chronic stress causes low levels of anabolic hormones like androgens and IGF-1 and prevents adiposity. As a result of nervous system activation regular increase in cortisol occurs. This anabolic-catabolic imbalance due to stress is related to abnormal processes leading to aging. Stress is also associated with obesity and insulin resistance. Prolong insulin resistance accelerates biological aging.

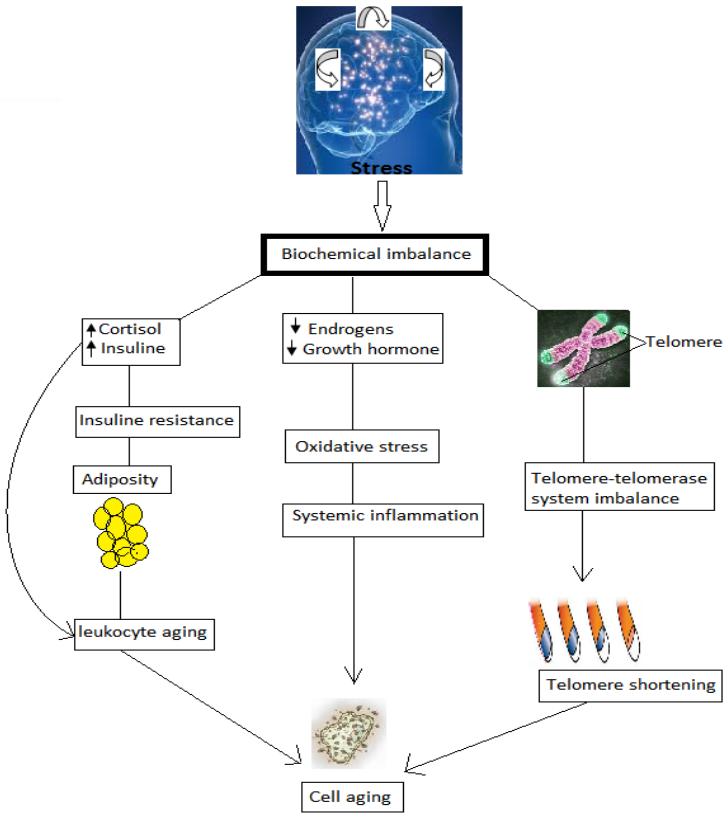

Figure 12: Schematic diagram of mechanisms underlying cellular aging due to stress.

The mechanism underlying cellular aging is telomere-telomerase maintenance system as illustrated in Figure 12. Eukaryotic chromosomes are capped with a protective nucleoprotein structure called telomeres. These are simple repeating sequence TTAGGG. While mitosis, with every cell division telomeres naturally get shortens due to end replication problem. DNA polymerase does not work properly at the end of DNA strand. Hence younger cells have longer telomere than older ones. During mitosis, before becoming consequences, cells undergo a limited number of cell divisions and then lose their ability of division and growth. Shortening of telomere causes end-to-end chromosome diffusion and ability of cell replenishment. Telomerase enzyme adds ups the telomere at the end of DNA with shorter telomere and hence promote cell life and a number of divisions. Chronic stressors, like oxidative stress, induced biochemical imbalance disturb this system and causes shortening of telomere by decreasing telomerase activity. Short telomere is associated with age related diseases like cardiovascular diseases, obesity, insulin resistance, diabetes, and Alzheimer and ultimately leading to death [31].

8. Seizures

Epilepsy is a diverse condition with multiple aetiologies that includes trauma, genetics, infection, neoplasms, and toxic exposures. The hypothalamic pituitary adrenal (HPA) axis have vital clinical insinuations to control seizures. Most of epileptic patients reported that their seizures are aggravated by stress. Seizure episodes occur repeatedly during high anxiety moments that are supposed to be irresistible [32]. During postictal period calcium level rose as compared to control subjects. Seizures incidence is high in epileptic patients having a high cortisol level. HPA axis is responsible to the arbitrate physiological response of the body to stress.

The activity of the HPA axis is controlled by a particular subgroup of parvocellular neurosecretory neurons in the paraventricular nucleus (PVN) of the hypothalamus. Corticotrophin-releasing hormone (CRH) neurons release CRH into the hypophyseal portal system that acts on the pituitary gland to indicate the release of ACTH. In humans the release of cortisol from the adrenal cortex is activated by ACTH. The stress response is controlled by numerous regulatory pathways. HPA axis are regulated by the negative feedback mechanism of glucocorticoids. Two type of mechanisms are involved in glucocorticoid signalling that are;

- Fast negative feedback mechanism
- Delayed negative feedback mechanism

In fast negative feedback mechanism non genomic actions are involved while delayed negative feedback mechanism involved genomic actions [33]. Two types of glucocorticoid receptors are involved in the mediation of these effects that are mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs).The connotation between stress and seizure activity is extensively acknowledged. The outcomes are controversial that alcohol intake, rebelliousness with antiepileptic drugs and sleep disturbances are related to stress. Mineralocorticoid receptors exerted the effect on Deoxy corticosterone (DOC) which is basically anticonvulsant. The threshold to induce seizure is induced by administration of DOC with picrotoxin and amygdala kindling. Potentiation of $GABA_A$ receptors caused the

mediation of anticonvulsant actions of DOC while these effects are eradicated by the usage of neurosteroid synthesis inhibitor, finasteride. Corticotrophin-releasing hormone (CRH) is also known as corticotrophin-releasing factor (CRF). It acts by two types of CRF receptors that are CRFR1 and CRFR2. Production of cAMP involves the activity of CRF on G-protein coupled receptors. Corticosterone (CORT) action is exerted by the activation of MRs and GRs [34].

Evidences show that in hippocampal sub regions, the actions of exogenous stress hormone are proconvulsant while the in vivo effects of stress hormones are intricate by the actions of hormones in multiple brain regions.

9. Discussion

Life now a day is more than a race. Stress may cause an individual to improve his or her abilities and compete in a better way or it may lead toward a downfall of abilities as well as health. But in the majority of cases it has negative effects on human personality as well as on health. Almost whole physiology is disturbed due to stress, which acts as the underlying cause of multiple disease of body from minor to major organs. Although life in this century is difficult, but one must try to avoid stress as much as possible. We must take some sort of healthy activities like walking, hanging out with family and friends. We must also have an awareness about stress and mental health. People usually avoid to consult a psychiatrist, but it must be practiced if our daily stress is leading toward sever condition. In order to spend a happy and healthy life we must take care whether the minor daily stressors are not taking us toward death.

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