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REVIEW ARTICLE

Stress, Oxidative Injury and Disease

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Abstract The living system on earth is largely using oxygen for burning metabolic fuel for energy. The toxicity of oxygen is largely due to the formation of free radicals in living systems. Stress is also responsible for the generation of free radicals. The evidence for the involvement of free radicals and oxidative injury in producing metabolic disturbance, maladjustment and many diseases has been accumulating since long. It is largely believed that the root cause of many chronic diseases is stress induced free radicals and resultant oxidative injury.

Keywords Oxidative stress · Reactive oxygen species · Free radicals

Introduction

The living system on earth is largely using oxygen for burning metabolic fuel for energy. The toxicity of oxygen was described as late as 1954 by Gershman in his free radical theory of oxygen. In 1956, Denham Harman proposed the concept of free radicals playing a role in the ageing process [1]. In 1969, McCord and Fridovich [2] discovered the enzyme superoxide dismutase (SOD) and provided the convincing evidence regarding the role of free radicals in living systems. In 1977, an Indian scientist settled in USA, Chandra Kant Mittal and his guide Prof. Murad [3] described the activation of enzyme, guanylate cyclase and formation of the "second messenger" cyclic guanosine monophosphate (cGMP) by hydroxyl radical ($^{\cdot}OH$).

During stress the free oxygen radicals increase due to high respiratory oxygen intake and metabolic turnover. Increased energy demand during stress caused by the adverse environmental conditions, severe physical work and psychological trauma (PTSD) require high oxygen intake to meet the energy demand. During such situations the organisms have to pay a price due to the generation of reactive oxygen species (ROS) as proposed by Halliwell and Gutteridge in 1993 [4]. Pro-inflammatory molecules are induced causing inflammation. Stress induced oxidative stress and inflammation play a major role in aging and development of various diseases. You name a disease; oxidative stress and/or inflammation are considered to be one of their causative factors. Some of the important diseases in which oxidative stress and inflammation play an important role are: coronary heart disease (CHD), hypertension, metabolic syndrome, diabetes, kidney dysfunction, pulmonary insufficiency, atherosclerosis, rheumatoid arthritis, inflammatory bowel disease, neurodegenerative diseases such as Alzheimer's and Parkinson's and age-related macular degeneration.

The formation of ROS also takes place as a result of exogenous stressors such as ultraviolet light, anoxia, environmental pollutants, ozone and oxides of nitrogen, cigarette smoke, and radiation. Endogenous production of free oxygen radicals takes place due to direct reduction of molecular oxygen by oxidases in the electron transport chain, phagocytes, D-amino acidoxidases, xanthine oxidase, epinephrine, coenzyme Q_{10}, and the cytochrome P_{450} systems [5]. Prolonged working hours, workload, fatigue, lack of sleep, psychological trauma and the impossible prospect of alleviating stress in human also cause oxidative injury as evidenced by significantly increased formation of 8-hydroxydeoxyguanosine (8-OH-dG), a marker of oxidative DNA damage [6].

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Some of the important pathways and reactions which generate free radicals have been reviewed by Valko et al. [7].

1. Mitochondria: Partially reduced oxygen is known to escape as superoxide radical in electron transport chain. The superoxide rapidly dismutates to form H_2O_2.
2. Auto-oxidation of reduced flavin, thiols, and small molecules such as hydroquinone and catecholamines.
3. Arachidonic acid pathway.
4. Endoplasmic reticulum and nuclear membrane electron transport systems.
5. Peroxisomes: potent source of cellular H_2O_2.
6. Respiratory burst: various types of stimulants such as opsonized bacteria, viruses, immunoglobulins, activated polymorphonuclear (PMN) leukocytes and macrophages, which take up large amount of oxygen and convert it into superoxide anion.
7. Transition metals, iron and copper, promote the generation of the most highly reactive class of active oxygen known as the hydroxyl radical.
8. Hypoxanthine and xanthine oxidase: activation of xanthine oxidase from xanthine dehydrogenase. Hypoxanthine [formed as a stepwise breakdown product of adenosine triphosphate (ATP)] is converted to xanthine and uric acid by xanthine oxidase when re-oxygenation occurs, giving rise to superoxides.

The active oxygen intermediates are also generated physiologically. These are produced in excessive amounts in pathologic situations and during exposure to stressful environmental insults. To protect the organism from deleterious effects of oxygen free radicals, a biochemical antioxidant defense system exists. It is essentially a two-component system;

1. Low molecular weight compounds quenching free radicals such as vitamins E, C, A, uric acid and glutathione.
2. Enzymes such as SOD, catalase, glutathione peroxidase, and glutathione S-transferase which metabolize free radicals to less reactive species.

Oxidative stress may arise due to deficiency in antioxidant compounds such as glutathione, uric acid, metal chelating agents [transferring, lactoferrin, ceruloplasmin], β-carotene, ascorbate, α-tocopherol. It may also arise due to decreased activity of antioxidant enzymes (SOD, catalase, glutathione peroxidase) and/or from increased formation of ROS. The highly reactive ROS can cause glutathione depletion, lipid peroxidation, membrane damage, DNA strand breaks, protein denaturation, and activation of proteases [8–10].

Stressful situations such as intermittent exposure of rats to hypobaric hypoxia (4,000 m) resulted in marked increase in thiobarbituric acid-reactive substances (TBARS) and significant decrease in Mn–SOD activity in soleus muscle, suggesting increased levels of oxygen free radicals and oxidative injury [11]. Work in high terrestrial altitudes and cold weather environment is accompanied by increased oxidative stress despite relatively high intakes of dietary supplemental antioxidants. High altitude exposure resulted in increased formation of reactive oxygen and nitrogen species (RONS) due to additional energy expenditure. This is often associated with increased oxidative damage of lipids, proteins and DNA. Exposure to high altitude appears to decrease the activity and effectiveness of antioxidant enzyme system. Moreover, during high altitude exposure several RONS generating systems are activated including mitochondrial electron transport chain, xanthine oxidase and nitric oxide synthase (NOS). The available information suggests that RONS are involved and are even the causative factor for acute mountain sickness. Supplementation with antioxidants seems to be necessary to prevent or decrease the oxidative stress at high altitudes [12].

During cold exposure, organisms generally up-regulate their metabolism. To sustain core body temperature in warm blooded organisms, an increase in metabolism is required immediately on exposure to low ambient temperatures. The elevation in metabolism may increase the production of ROS much before induction of the antioxidant protection and repair mechanisms. The effect of acute (6 h, 6 °C) and chronic cold (21 days, 6 °C) exposure on the activities of Cu–Zn–SOD, Mn–SOD and Catalase in the rat brown adipose tissue (BAT), an important site of cold-induced thermogenesis, was investigated. The activity of SOD in BAT was reduced in rats after acute (6 h) cold exposure compared to the levels of unexposed and chronic (21 day) cold-exposed animals. The disparity between ROS production and the protection and repair mechanisms was at its greatest during acute cold exposure. This may result in a significant risk of oxidative stress [13].

Cold injury is a tissue trauma produced by even brief exposure to a severely cold and windy environment. Re-warming of frozen tissue is associated with blood reperfusion and the simultaneous generation of free oxygen radicals. On re-warming, the free fatty acids are metabolized via cyclo-oxygenase. The adenine nucleotides are metabolized via the xanthine oxidase pathway. Both these paths may be the source of free oxygen radicals [14].

High environmental temperatures challenge the animal's ability to maintain energy, thermal, water, hormonal and mineral balance. It has been hypothesized that hyperthermia promotes oxygen-centered free radical formation in cells. Heat stress stimulates excessive production of free radicals (superoxide anion radicals, hydroxyl radical, hydrogen peroxide and singlet oxygen) which are continuously produced in the course of normal aerobic metabolism. Using electron paramagnetic resonance (EPR) spin trapping, direct

evidence for free radical generation during hyperthermia in intact, functioning cells was studied. Rat intestinal epithelial cell monolayers were exposed to 45 °C for 20 min, after which the nitrone spin trap 5, 5-dimethyl-1-pyrroline *N*-oxide (DMPO) was added. Compared to control cells at 37 °C, heat-exposed cells had increased free radical EPR signals consistent with the formation of DMPO/$^{-}$OH. These findings indicate that the heat increases the flux of cellular free radicals and support the hypothesis that increased generation of oxygen-centered free radicals and the resultant oxidative stress may mediate in part, heat-induced cellular damage [15]. A single mild transient scrotal heat stress exposure (40 or 42 °C for 30 min), in mouse testes resulted in complex stress response including induction of genes associated with oxidative stress and hypoxia [16]. This further confirmed that heat stress resulted in oxidative stress.

Immobilization stress or disuse of muscles has also been indicated to cause oxidative stress [17].The movements of trace elements and the level of oxidative stress in the soleus, a typical slow red muscle, atrophied by immobilization, were investigated at different intervals. Male Wistar rats (14 weaks old) whose one ankle joints were immobilized in the extended position were killed after 4, 8, and 12 days. Fe^{++}, Zn^{++}, Mn^{++}, and Cu^{++} concentrations, the levels of TBARS and glutathione were measured. The rate of atrophy increased rapidly until the 8th day and slowly after that. In whole muscle, Fe concentration kept increasing, and Zn^{++} and Mn^{++} increased temporarily. Increased TBARS and glutathione disulfide and decreased total glutathione indicated the increased oxidative stress during atrophy. This might have resulted from an increased Fe level especially that of the microsomal fraction. Vitamin E injection lessened the rate of atrophy, which suggested that oxidative stress accelerated muscle atrophy. This might be mediated by increased intracellular Ca^{++}. Also metallothionein was induced in muscle atrophy [18].

Free radicals are helpful for some of the biological functions such as phagocytosis. ROS destroy invading microorganisms by a process commonly referred to as respiratory burst. However, an imbalance between production of ROS and antioxidant defense can result in an oxidative stress, which may lead to a variety of biochemical and physiologic changes often resulting in metabolic impairment and cell death.

Stress and Immunity

It is a common observation that stressed individuals suffer and succumb easily to infection. Common belief is that stress invariably leads to suppressed immunity. Stress increases the secretion of glucocorticoids and catecholamines and to some extent prolactin, growth hormone and nerve growth factor. Stress, through the action of these hormones, has detrimental effect on immune function including reduced NK cell activity, lymphocyte populations, lymphocyte proliferation, antibody production and reactivation of latent viral infections. Such effects on the immune system have severe consequences on health [19].

Stress influences the immune system through two routes; the hypothalamus–pituitary–adrenal (HPA) axis and the autonomic nervous system. The endocrine and immune systems are integrated through a bidirectional network in which hormones affect immune function and, in turn, immune responses are reflected in neuroendocrine changes. This bidirectional communication is possible because both systems share a common "chemical language" that results from sharing of common ligands (hormones and cytokines) and their specific receptors. Cytokines are important partners in this crosstalk. They play a role in modulating the HPA axis responses at all the three levels: the hypothalamus, the pituitary and the adrenals. Acute effects of cytokines are seen in the central nervous system, particularly the hypothalamus. The effect on pituitary and adrenals take effect during prolonged exposure such as during chronic inflammation and infection. The three "inflammatory cytokines", tumor necrosis factor-α (TNF α), interleukin-1 (IL-1), and interleukin-6 (IL-6) cause stimulation of the HPA axis in vivo, alone, or in synergy with each other. This is mediated through stimulation of hypothalamic CRH and AVP secretion and by direct effects at the pituitary and adrenocortical levels. IL-6, the main endocrine cytokine, causes major elevations of ACTH and cortisol.

The response of the immune system differs with the type of stress, intensity, duration, and the condition of the organism receiving the stress. Stress-induced changes in blood leukocyte numbers are characterized by a significant decrease in numbers and percentages of lymphocytes and monocytes, and by an increase in numbers and percentages of nutrophils. Absolute numbers of peripheral blood T cells, B cells, NK cells, and monocytes all show a rapid and significant decrease (40–70 % lower than baseline) during stress. Thus, stress conditions that cause a significant and sustained activation of the HPA axis leads to a decrease in blood leukocyte numbers. However, an acute stress response may include a biphasic change in blood leukocyte numbers. Soon after the beginning of stress (order of minutes) or during mild acute phase or exercise, catecholamines and neurotransmitters induce the leukocytes to exit from spleen, lung, and other organs and enter the blood vessels and lymphatic. This would result in an increase in blood leukocyte numbers; the effect being prominent in NK cells and granulocytes. As the stress continues, activation of the HPA axis further leads to the release of glucocorticoid hormones inducing leukocytes to exit the blood and take position at such as skin, lung, gastrointestinal (GI), urinary-genital tracts, mucosal surfaces, and lymph nodes. These changes in immune cells population is in preparation for

stress challenge. Such a redistribution of leukocytes would result in a decrease in leukocyte numbers in circulation [20].

Stress is very well known to suppress immune function and increase susceptibility to infections. Paradoxically, stress is also known to exacerbate asthma and other allergic, autoimmune and inflammatory diseases. Moreover, the short-term fight-or-flight stress response is one of nature's fundamental defense mechanisms that enables the cardiovascular and musculoskeletal systems to promote survival and it is unlikely that this response would suppress immune function at a time when it is most required for survival (e.g. in response to wounding and infection by a predator or aggressor). These observations suggest that stress may suppress immune function under some conditions while enhancing it under others. The effects of stress are likely to be beneficial or harmful depending on the type of immune response (immune-protective, immune-regulatory/inhibitory, or immunepathological). Studies have shown that several critical factors influence the direction (enhancing vs. suppressive) of the effects of stress or stress hormones on immune function;

1. Duration (acute vs. chronic) of stress: Acute or short-term stress experienced at the time of immune activation can enhance innate and adaptive immune responses. Chronic or long-term stress can suppress immunity by decreasing immune cell numbers and function and/or increasing active immunosuppressive mechanisms (e.g. regulatory T cells). Chronic stresses can also deregulate immune function by promoting proinflammatory and type-2 cytokine-driven responses.
2. Effects of stress on leukocyte distribution: Compartments that are enriched with immune cells during acute stress show immune-enhancement while those that are depleted of leukocytes, show immune-suppression.
3. The differential effects of physiologic versus pharmacologic concentrations of glucocorticoids, and the differential effects of endogenous versus synthetic glucocorticoids: Endogenous hormones in physiological concentrations can have immune-enhancing effects. Endogenous hormones at pharmacologic concentrations and synthetic hormones are immunosuppressive.
4. The timing of stressor or stress hormone exposure relative to the time of activation and time course of the immune response: Immunoenhancement is observed when acute stress is experienced at early stages of immune activation, while immune-suppression may be observed at late stages of the immune response [21].

Stress and Inflammation

The inflammatory processes may be defined as a sequence of events that occur in response to noxious stimuli, trauma or infection. These responses are orchestrated by a highly modulated interaction between mediators of inflammation and inflammatory cells. Cytokines represents a group of multifunctional substances that are involved in many steps of the inflammatory response. Generally cytokines can be classified as pro- or anti-inflammatory, depending on the way they influence inflammation. In a more simplified view, pro-inflammatory cytokines (e.g. IL-1β, TNF α, IL-6, and IL-19) seem to be involved in the initiation and amplification of the inflammatory processes, whereas the anti-inflammatory cytokines viz. IL-10, TGF-β, and IL-1 receptor antagonist (IL1-Ra) negatively modulate these events [22].

Inflammation is a two-edged sword. In acute situations and at low levels, it deals with the abnormality and promotes healing. When chronically sustained at high levels, it can seriously damage viable host tissue. Biochemically, the intensity of their activation is related to a spectrum of inflammatory mediators. The known spectrum includes, but is not limited to, prostaglandins, complement components, anaphylotoxins, cytokines, chemokines, proteases, protease inhibitors, adhesion molecules and free radicals.

NF-κB activation has been implicated in a wide variety of diseases, including cancers, diabetes mellitus, cardiovascular diseases, autoimmune diseases, viral replication, septic shock, neurodegenerative disorders, arthritis, asthma, inflammatory bowel disease, and several other inflammatory conditions. Furthermore, the oxidized lipids from the low density lipoproteins associated with atherosclerosis activate NF-κB which then activates other genes. NF-κB is activated by many divergent stimuli including pro-inflammatory cytokines (e.g., TNF-α, IL-1), T- and B cell mitogen, bacteria, lipopolysaccharides (LPS), viruses, viral proteins, double-stranded RNA, and physical and chemical stresses. Cellular stresses, including ionizing radiation and chemotherapeutic agents, also activate NF-κB. Once NF-kB is activated, it causes the expression of almost 500 different gene products that includes enzymes, cytokines, adhesion molecules and other signaling intermediates closely linked with inflammation. TNF is one of the most potent activators of NF-κB. Experimental animal viz. mice that are susceptible to atherosclerosis exhibit NF-κB activation when fed an atherogenic diet. In the light of these findings, the abnormal activation or expression of NF-κB is believed to be associated with a wide variety of pathologic conditions.

Stress and Metabolism

Various threatening stress stimuli, such as pain, low blood pressure and/or infection elicit a set of neuroendocrine responses that include an increased secretion of

catecholamines and glucocorticoid from the adrenal gland and activation of the sympathetic nervous system. These hormone secretions allow a 'fight or flight' response by mobilizing endogenous substrate. They also exert anti-insulin actions and may, in the long term, induce a state of insulin resistance. In addition, stress stimulates inflammatory mediators in mononuclear cells. Given the possible role of low-grade inflammation in chronic metabolic disorders, stress may be a factor in the development of insulin resistance and the metabolic syndrome [23].

Long-term administration/secretion of glucocorticoids such as in Cushing syndrome is associated with visceral obesity, insulin resistance, hypertension, and elevated cholesterol and triglyceride levels. Thus, hypercortisolism resembles the "metabolic syndrome X" (MS-X) in both its somatic and biochemical phenotypes. MS-X has been recently associated with increased urinary free cortisol excretion suggesting that glucocorticoids may represent a common denominator for this state. Moreover, both hypercortisolism and MS-X are associated with increased atherosclerosis, resultant cardiovascular morbidity and mortality. The association between chronic experimentally induced psychosocial stress and hypercortisolism/MS-X-like state with increased incidence of atherosclerosis was recently reported in cynomolgus monkeys. In these animals, chronic, stress induced activation of the HPA axis and therefore hypercortisolism apparently leads to visceral obesity, insulin resistance and suppression of growth hormone secretion all converging to the development of varying degrees of the physical and biochemical phenotype of the "MS-X".

Low turnover osteoporosis is almost invariably seen in association with hypercortisolism, adult GH deficiency and the chronic stress model mentioned above. It further reflects the detrimental effect of the combination of high cortisol and low GH and/or IGF-I concentrations at the level of the osteoblasts. Osteoporosis may be further potentiated by the stress-related hypogonadism and could be responsible for the increased prevalence of osteoporosis refractory to estrogen replacement in depressed menopausal woman.

Stress and Aging

The process of ageing may be defined as a progressive decline in the physiological functions of an organism after the reproductive phase of life. Aging affects most of the body functions such as: loss of hearing, loss of body fats under the skin, decrease in amount of body water, sluggish liver and kidney functions, GI problems, loss of muscle strength, decline in sexual hormones and sexual function, decreased sensation and taste, changes in cardiovascular and respiratory systems, decreased oxygen and nutrient supply to body, decrease in bone strength and density, decreased visual abilities with or without macular degeneration, decreased neural function, memory and learning etc. It is not necessary that such effects of ageing are observed in each and every case to the same extent, yet, by and large, the deterioration in sensory functions and resistance to infection, recovery from injuries and inflammation are invariably affected. One of the favored theories as the cause of ageing is the Free Radical Damage Theory [24].

Free radicals cause damage to the macromolecular components of the cell, giving rise to accumulated damage to cells eventually organs to slow/stop function (1). Telomere shortening is affected by oxidative damage [25]. Since stress accelerates the oxidative damage through free radicals, it might lead to accelerated ageing.

Various rejuvenating Rasayana in Ayurvedic system of Indian medicine deal with prevention, amelioration and cure of geriatric ailments by increasing overall body immunity fighting infections, inactivating antigens and preventing carcinogenic mutations. Triphala a specific polyherbal preparation, consisting of equal amounts of fruits of three plants, namely *Terminalia chebula* Retz. *Terminalia bellirica* Roxb and *Emblica officinalis* Gaertn, in fine powder form, has both anti-oxidative and anti-inflammatory properties. It has been specifically mentioned in traditional Ayurvedic texts for its beneficial effects in geriatric diseases.

Respiratory Diseases

There is substantial evidence that oxidative stress plays an important role in the injurious and inflammatory responses in airways diseases such as asthma and chronic obstructive pulmonary diseases (COPD). In addition, pro-inflammatory reactions as a result of oxidative stress and other protective mechanisms such as the up-regulation of protective anti-oxidant genes also take place. Oxidative stress is a fundamental factor in the inflammation occurring in these diseases [26].

Cardiovascular Disease

Repeated episodes of acute and/or chronic psychological stress may induce a chronic inflammatory process culminating in atherosclerosis. These inflammatory events may account for approximately 40 % of atherosclerotic patients with no other known risk factors. Stress, by activating the sympathetic nervous system, the HPA axis, and the renin–angiotensin system, causes the release of various stress hormones such as catecholamines, corticosteroids,

glucagon, growth hormone, and renin. The elevated levels of homocysteine induce a heightened state of cardiovascular activity injuring endothelium. Further, it induces the adhesion molecules in endothelial cells recruiting inflammatory cells to adhere and translocate to the arterial wall. An acute phase response, similar to that associated with inflammation is also characterized by macrophage activation, the production of cytokines, other inflammatory mediators, acute phase proteins and mast cell activation. All of these promote the inflammatory process. Stress also induces an atherosclerotic lipid profile with oxidation of lipids that may result in arterial thromboses [27].

In the development of CHD, pro-inflammatory cytokine IL-6 plays a key role. In fatty streaks and in the atheromatous regions, the macrophage foam cells and smooth muscle cells (SMC) express IL-6, suggesting a role for this cytokine along with IL-1 and TNF-α, in the progression of atherosclerosis. Both of these cytokines induce the release of IL-6 from several cell types including SMC. During vascular injury, SMC are exposed to platelets or their products. The cytokine production by SMC further contributes to vascular damage. Furthermore, circulating IL-6 stimulates the HPA axis [28].

Hypertension

Animal studies have shown that oxidative stress and renal tubule interstitial inflammation are associated with and have a major role in the pathogenesis of hypertension. Conversely, hypertension has been shown to cause oxidative stress and inflammation in renal and cardiovascular tissues in experimental animals. Taken together, these observations indicate that oxidative stress, inflammation and arterial hypertension participate in a self-perpetuating cycle which, if not interrupted, can lead to progressive cardiovascular disease and renal complications [29].

Neurological Disorders

Brain aging is associated with a progressive imbalance between antioxidant defenses and intracellular concentration of ROS as exemplified by increases in products of lipid per-oxidation, protein oxidation, DNA oxidation, oxidative damage to mitochondrial DNA and the electron transport chain, perturbations in brain iron and calcium homeostasis and changes in plasma cysteine homeostasis.

Stress induced chronic inflammation is associated with a broad spectrum of neurodegenerative diseases of aging, including Alzheimer's disease (AD), Parkinson's disease (PD) and age-related macular degeneration. The brain is particularly vulnerable to oxidative damage because of its high oxygen utilization, its high content of polyunsaturated fatty acids and the presence of redox-active metals (Cu, Fe). Oxidative stress increases with age and therefore it can be considered as an important causative factor in several neurodegenerative diseases, typical for older individuals.

Kidney Disease

Evidence indicates that increased oxidative stress in kidney and resultant inflammation may mediate in the kidney pathology. Further, surrogate indexes of atherosclerosis such as intima-media thickness and aortic pulse wave velocity have been demonstrated to be related to plasma concentration of markers of endothelial activation, inflammation and fibrosis in patients with different stages of chronic kidney disease (CKD). Inflammation and oxidative stress may contribute to cardiovascular risk in CKD patients [30].

Diabetes

Relatively small amounts (10 %) of patients suffering from diabetes mellitus have type 1 or insulin dependent diabetes. However, the majority of diabetes patients are non-insulin-dependent and capable at least initially of producing insulin but are deficient in their cellular response. This type of diabetes is the type 2 diabetes mellitus. It is the most common form of diabetes. Decreased uptake of glucose into muscle and adipose tissue leads to chronic extra-cellular hyperglycemia resulting in tissue damage and pathophysiological complications, involving heart disease, atherosclerosis, cataract formation, peripheral nerve damage, retinopathy and others. Increased oxidative stress has been proposed to be one of the major causes of the hyperglycemia-induced trigger of diabetic complications. Hyperglycemia in an organism stimulates ROS formation from a variety of sources. These sources include oxidative phosphorylation, glucose auto-oxidation, NAD (P) H oxidase, lipooxygenase, cytochrome P_{450} monooxygenases and NOS. Since increased gluconeogenesis is a characteristic feature of the "fight or flight" response and glucocorticoids induce insulin resistance, activation of the HPA axis may contribute to the poor control in diabetic patients during periods of emotional stress, inflammation and other diseases. Indeed, activation of the HPA axis has been demonstrated in type II diabetic patients.

Gastrointestinal Function and Inflammatory Bowel Disease (IBD)

Several studies suggest that the stress influences GI function. During stress, gastric emptying is delayed while

colonic motor activity increases in animals and humans. Innervations by the vagus nerve and the peripheral limbs of autonomic nervous system provide the network for rapid responses of the GI system to stress. In addition, the direct secretion of a number of neuropeptides, such as somatostin and vasoactive intestinal peptide (VIP), in the vascular system supply of the GI tract, provide a direct link with the neuroendocrine and, perhaps, to the immune system. CRH microinjected into the PVN was shown to reproduce the stress responses of the GI system in the animal model: CRH inhibited gastric emptying and stimulated colonic transit and fecal excretion. This effect was abolished by the intrathecal administration of a CRH-antagonist. It appears that these selective responses of the GI motor function to PVN CRH-gastric stasis and increased colonic motility are mediated through the simultaneous inhibition of the vagus nerve and stimulation of the sacral parasympathetic system by CRH and the LC/noradrenergic neurons, observed during the stress of surgery and/or anesthesia. IL-1β, a potent cytokine that is found to be increased during surgery and in the immediate postoperative period, inhibits gastric motility. Administration of CRH antagonist prevented the surgery-induced rise of IL-1β in rats suggesting that CRH may be the mediator for IL-1β-induced gastric stasis.

Irritable Bowel Syndrome (IBS)

IBS is a functional disorder of the lower intestinal tract without structural pathology. IBS is characterized by episodic abdominal discomfort, bloating, and alteration of bowel habits with no definite cause currently known to the medical field. Research suggests that the GI tract and the mind are closely linked and for many people who suffer from irritable bowel syndrome (IBS), the symptoms are often exacerbated by stressful or emotional life events. One review points out that people with IBS may be more likely than the general population to experience a heightened stress response, poor coping skills, psychosocial fears, and co-morbid mood disorders [31]. The inflammation in intestinal epithelial tissue has also been co-related with the disease.

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints and tissue around the joints with infiltration of macrophages and activated T cells. The pathogenesis of this disease is linked predominantly with the formation of free radicals at the site of inflammation. Oxidative injury and inflammatory status in various rheumatic diseases has been confirmed by increased levels of isoprostanes and prostaglandins in serum and synovial fluid of arthritic tissue as compared to controls. Oxidative status in synovial tissue was also associated with a higher incidence of p53 mutations [32]. The development of mutations in the p*53* tumor suppressor gene and other key regulatory genes could help convert inflammation into chronic disease in rheumatoid arthritis and other inflammatory disorders [33].

Cancer

Stress induced oxidative stress may increase cellular redox imbalance. This has been found in various cancer cells as compared with normal cells; the redox imbalance may be related to oncogenic stimulation. Permanent modification of genetic material resulting from "oxidative damage" represents the first step in mutagenesis, carcinogenesis and ageing. DNA damage can result in either arrest or induction of transcription, induction of signal transduction pathways, replication errors and genomic instability; all of which are associated with carcinogenesis [34].

Occupational exposure to asbestos containing about 30 % (weight) of iron was related to increased risk of asbestosis, the second most important cause of lung cancer [35]. Occupational exposure to cadmium has been associated with occurrence of increased oxidative stress and cancer [36]. Arsenic compounds are well-established human carcinogens [37]. Tobacco smoke, a well known carcinogenic source of ROS, increased the oxidative DNA damage rate by 35–50 %, as estimated from the urinary excretion of 8-OH-G, or by 20–50 %, estimated from the level of 8-OH-G in leukocytes [38].

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