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REVIEW ARTICLE

Physiology of stress and the involvement of reactive oxidative species: A mini-review

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ABSTRACT

Stress is evident amongst all organisms as a part of their life. It triggers various neurohormonal changes to restore homeostasis. Physiological responses and psychological changes occur during stress. The hypothalamic pituitary adrenal (HPA) axis and sympathetic nervous system (SNS) play a major role in response to stress. SNS acts via norepinephrine through subcortical activation of the locus coeruleus. Reactive oxygen species (ROS) are the derivatives of oxygen, which produce free radicals. The cell membrane contains a high level of unsaturated fatty acids that is damaged by ROS oxidation. Protein damages occur directly or indirectly by ROS by fragmentation, peroxidation, structural changes, proteolysis and formation of cross-linkages. ROS can damage DNA bases and deoxyribose sugars; cause purine losses, DNA strand breaks, DNA-protein cross-linkages and harm to the DNA repair mechanism. Higher levels of ROS lead to disease states. Understanding the mechanisms and significance of ROS involving pathways may help to reveal therapeutic strategies for diseases.

Keywords

Hypothalamic pituitary adrenal axis, reactive oxygen species, stress, sympathetic nervous system

Introduction

The term stress was first coined by Hans Selye in 1936, who defined it as "the non-specific response of the body to any demand for change". Stress is a state of physical, mental or psychological reactions to demanding circumstances. A number of different physiological responses and psychological changes takes place e.g fear, an increase in heart rate and blood pressure along with intensified alertness. [1] Autonomic nervous system, cardiovascular and the immune system play an active role by altering the different biochemical and cellular activities to combat stressed situations. [2, 3] Stress triggers an increase in biosynthesis of Corticotrophic Releasing Hormone (CRH) in the paraventricular nucleus (PVN) amygdala and frontal cortex. Amygdala and the limbic cortex of brain secrete CRH which finally releases Adrenocorticotrophic hormone (ACTH) into the bloodstream and is responsible for the production of more cortisol. [4] Stress can also influence higher functions like learning and memory. [5, 6] Higher stress levels are associated with increased risk of heart attacks and strokes. Altered inflammatory reaction in stress affects the immune system, making it weaker. Insomnia is another important issue in stressed individuals. Stress leads to depression and anxiety, deteriorating health of the individuals.

The stress system is crucial for the survival of the individual and species. Eustress is an important part of life for the mental and physical well being. The improper functioning of the stress system causes pathophysiological responses. Stress activates a complex behavioural and physiologic response in the human body. [7] The concept of stress did not originate from the field of the medical or biological sciences; it was from the field of engineering where stress means physical pressure applied to a structure. [8] According to the concept of biological science, stress means a complex condition, when the homeostasis of an organism is imbalanced. To be clearer, the response to combat stress is an integrative part of the system to restore homeostasis. Activation of a neuro-endocrinological response is observed during stress. Stress is a psychophysiological process associated with a negative emotional state, physical threat, or distress. Stress affects a number of systems - autonomic, cardiovascular, and immune systems. [2, 3] Whereas, stressors are the conditions that endanger or are perceived to endanger, the survival of an individual. [9]

Mechanisms of the stress response: Physiological and neurohormonal basis.

Although hypothalamic pituitary adrenal (HPA) axis and autonomic activities serve different physiological functions, they overlap in response to stress. The sympathetic nervous system (SNS) plays a major role in response to stress by releasing norepinephrine through subcortical activation of the locus coeruleus (Figure – 1).

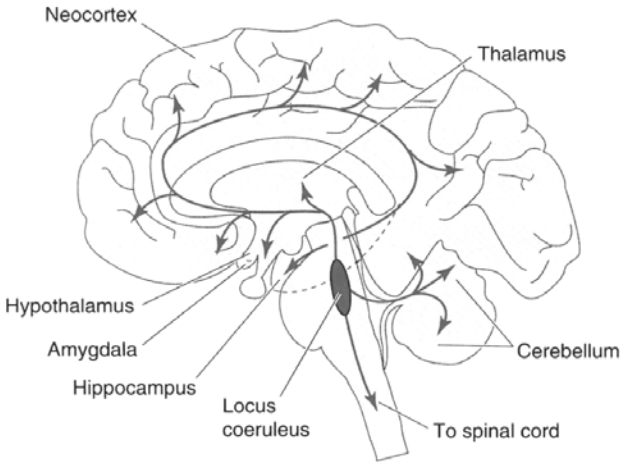

Figure – 1 shows the location of locus coeruleus nucleus, which is a deeper structure in the pons, sending noradrenergic projections to different brain regions.

Automatic nervous system (ANS) response: the fast response

The sympathetic nervous system (SNS) is responsible for the fight-or-flight response. In response to stress, the locus coeruleus norepinephrine (LC-NE) system sendsneural impulses to the adrenal medulla to release catecholamines (epinephrine and norepinephrine), with immediate action to burn carbohydrate resources for an increase in cellular activity. [10] Cellular metabolisms are accelerated and physiological changes occurring in important organ systems are directly linked to survival. For instance, increased cardiovascular activity, enlargement of the pupils, bronchodilation, and constriction of peripheral blood vessels and splanchnic vascular bed for better perfusion of vital organs. Due to increase in the epinephrine drive, the liver releases carbohydrate, replenish increased energy consumption, which is directly linked to survival. [11]

HPA Axis: Slow Response

Hypothalamus releases CRH which acts on the anterior pituitary to release ACTH, a potent stimulator for the release of cortisol from the adrenal gland. A feedback mechanism controls higher or lower secretions. The HPA axis is actively involved in the stress mechanism when the stimulus continues for a prolonged time. (Figure – 2). [12]

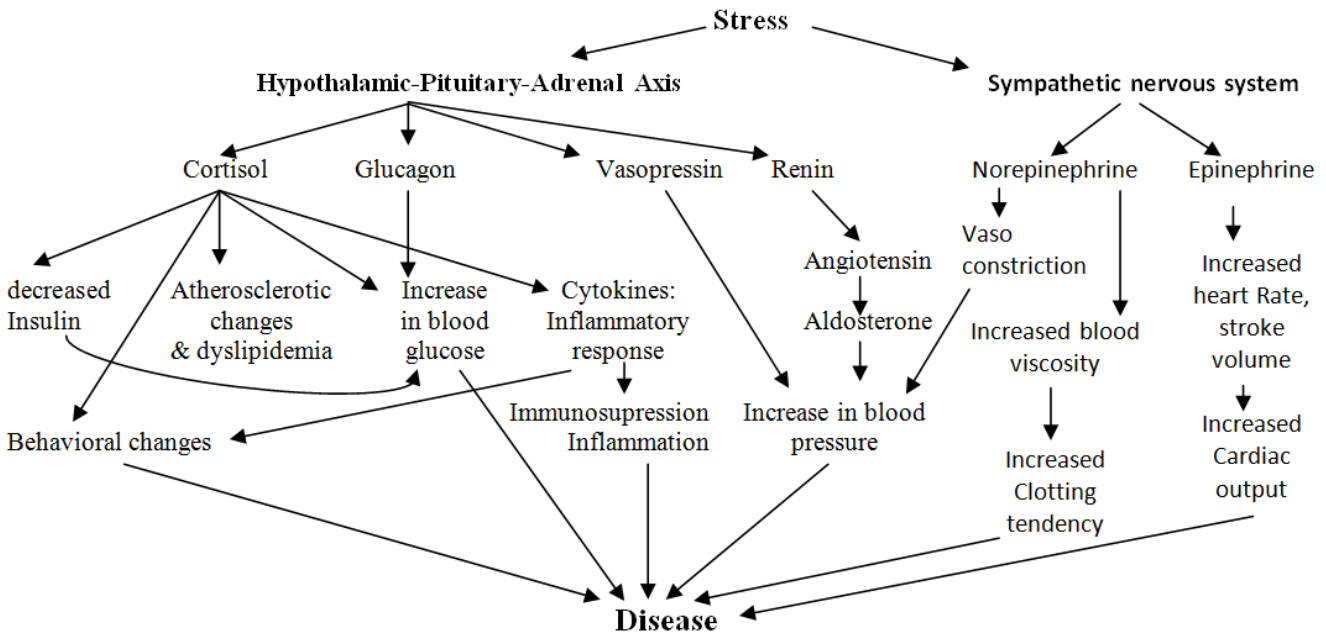

Figure – 2 Stress can influence HPA and the sympathetic nervous system. In the HPA axis cortisol is released, which exerts influence on a number of biochemical pathways leading ultimately to disease. The sympathetic nervous system releases epinephrine and norepinephrine which acts on the cardiovascular system increasing blood pressure and initiatinga clotting mechanism - a cause of pathophysiology.

In stressed situations, the brain becomes alert, evident by signals from the amygdala and higher cortex; a higher quantity of CRH is released by the PVN of the hypothalamus results in increased release of ACTH into the bloodstream. As ACTH level increases in the blood, it activates adrenal cortex to produce an enormous amount of cortisol and also stimulates hepatic gluconeogenesis. [4] Resultant neurological changes such as learning and memory, along with immunological changes like lymphatic responses are well documented. [5, 6]

HPA axis acts as a self-regulating system, which prepares to combat with the stressed situations by changing the cellular activities in the response of cortisol surge. [13] Binding of a higher level of cortisol compared to normal to the hippocampal glucocorticoid receptors and PVN level causes negative-feedback regulation of the HPA axis. [14]This restores homeostasis by a decrease in cortisol output. [15] If any dysregulation occurs in the HPA axis, constant release of elevated cortisol damage hippocampal neurons. [16] Stress strongly influences the endocrine, haemopoietic and immune systems, where cytokines and cortisol plays a vital role in the communication. [17-19]

Oxidative stress

The terminology indicates a condition of oxidative damage arising due to increase in free radical generation and less potent antioxidant system which causes damage to the biomolecular structures such as DNA, RNA, lipids, and proteins. [20, 21] There are several causes of short-term oxidative stress in tissue levels such as trauma, infection, thermal injury, exposure to toxic substances, and vigorous exercise. In these conditions, there is an increase in oxidative enzymes e.g., xanthine oxidase, lipoxygenase, cyclooxygenase which generates free radicals, increased phagocytic activity, release metal ions (Fe++, Cu++) and affect the electron transport chains. ROS is associated with the progression of diseases like cancer, diabetes mellitus, Parkinson's disease etc. [22]

Stress and ROS

ROS are molecular species, derivatives of oxygen, which produces free radicals more reactive than molecular oxygen. Free radicals are atoms or molecules containing an impaired number of electrons. Superoxide ($O_2^{\cdot -}$) radicals and nitric oxide (NO.) radicals are generated inside the cell. Generally, 2% of consumed oxygen produces $O_2^{\cdot -}$ by means of mitochondrial respiration and phagocytosis. [23] Some conditions increase ROS generations, such as infections, exercise, pollutions, exposure to UV light and ionizing radiation. ROS acts as the fundamental oxidants able to alter cellular and metabolic structures. They interact with unsaturated fatty acids, proteins, and polysaccharides and cause a change in the DNA strand, leading to mutations. [24, 25]

Free radicals production in the human body

Formation of free radicals in the human body is a continuous process by means of enzymatic and nonenzymatic reactions. ROS and free radicals are mainly produced during the biochemical reactions during normal physiological mechanisms. Other important factors include exposure to X-rays, chemical pollutants, ozone, certain drugs, pesticides, air pollution and smoking. [26]

Contributors of generation of free radicals are nitric oxide and O2.− radicals.

Nitric oxide synthase enzymes produce NO., a well-known endothelial relaxing factor. ROS generation involves complex transformation reactions. NO. and O2.− radicals produce hydroxyl radicals (˙OH), alkoxy radicals (RO.), peroxyl radicals (ROO.), singlet oxygen (O2*). A few of the free radicals are transformed into hydrogen peroxide (H2O2), peroxynitrite (ONOO.), hypochlorous acid (HOCl), which in turn facilitates ROS production. [27, 28]

ROS induced oxidative damages

ROS reactions produce a variety of secondary radicals which are converted by oxygen into critical peroxyl radicals and involve in chain reactions causing cellular damage. [23]

Membrane damage: Cell membrane is prone to damage by ROS oxidation, because of a higher level of unsaturated fatty acids as a structural component. ROS causes lipid peroxidation, generation of lipid hydroperoxide (LOOH) which further produces malonaldehyde, 4-hydroxy nonenal (4-HNE) or form cyclic endoperoxide, isoprostanes, and hydrocarbons. Cross-linking of membrane proteins, alteration in cell membrane viscosity and generation of lipid-protein and lipid-DNA adducts damage the cell. [29]

Effects on proteins and amino acids: Protein damages occur directly or indirectly by ROS by fragmentation, peroxidation, structural changes, proteolysis and formation of cross-linkages. Amino acids containing tryptophan, cysteine, and methionine as side chain residues are most vulnerable to ROS oxidation. Aldehydes and ketones produced during the oxidation of protein cause oxidative stress. They are associated with progression of diseases e.g. neurodegenerative disorders, diabetes, hypertension, atherosclerosis, inflammation. [29, 30]

DNA damage: Even though DNA is a stable structure, ROS can damage DNA bases, cause DNA-protein cross-linkages, break strands of DNA, purine loss, deoxyribose sugar damage, and harm to the DNA repair system. All ROS are not responsible equally for DNA damage. When ˙OH radical interacts with DNA, diverse adducts form which contributes significantly to mutations. The prime target of ˙OH radical is purine and pyrimidine bases producing ˙OH radical ad-ducts, which modifies the DNA bases and causes their release. 8-hydroxydeoxyguanosine (8-OH-dG), 8 (or 4-, 5-)-hydroxyadenine, thymine peroxide, thymine glycols and 5-(hydroxymethyl) uracyl-5 are considered as crucial base modifications. Sugar moieties are also damaged by ROS, producing sugar peroxyl radicals which break DNA strands. Devastating consequences occur due to DNA damage that includes mutations, carcinogenesis, ageing and cell death. [31]

Conclusion

Stress system is crucial for the survival of the individual and species. The improper functioning of the stress system causes pathophysiological responses. Activation of a neuro-endocrinological response is observed during stress. Although hypothalamic pituitary adrenal (HPA) axis and autonomic activities serve different physiological functions they overlap in response to stress. ROS produces free radicals which cause membrane damage, fragmentation, peroxidation, structural changes in proteins and proteolysis. DNA damage by ROS includes mutation, carcinogenesis, ageing and cell death. Understanding the mechanism and significance of ROS involving pathways may help to reveal therapeutic strategies for diseases.

Abbreviations

8-hydroxydeoxyguanosine (8-OH-dG), Adrenocorticotrophic hormone (ACTH), automatic nervous system (ANS), Corticotrophic Releasing Hormone (CRH), hypothalamic pituitary adrenal (HPA) axis, lipid hydroperoxide (LOOH), locus coeruleus norepinephrine (LC-NE), nitric oxide (NO), paraventricular nucleus (PVN), sympathetic nervous system (SNS)

Competing interests

None declared.

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