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Review Article

Human Stress and Hormonal Responses

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Abstract

There are several hormones secreted in the human while we experience stress. They are adrenalin, noradrenalin and cortisol. These hormones are designed to deal with us in stressful situations by increasing our heart-beat, sugar level and blood pressure. They provided us with energy and strength to either flight or fight tactfully. While adrenalin makes the heart beat faster causing enhanced blood pressure, cortisol increases the level of sugar in blood for brain's use. This is a normal phenomenon of stress responses in humans. But, long-term abuse of these chronic stresses when persist may put humans at higher risk of many health problems. The present paper deals with the study of stress hormonal responses in humans.

Keywords: *Human Stress Hormones; HPA; Cortisol; Blunted CAR; Endocrine Disorders; Diseases*

Abbreviations

HPA: Hypothalamus-Pituitary Adrenal Axis; CAR: Cortisol Awakening Response; CRH: Cortisol Releasing Hormone; IBS: Irritable Bowel Syndrome; TSH: Thyroid-Stimulating Hormone; SAA: Salivary Alpha-Amylase; C_gA: Chromogranin A; I_gA: Immunoglobulin A; FGF-2: Fibroblast Growth Factor-2; ACTH: Adrenocorticotropic Hormone

Introduction

Stress is now an unavoidable hidden factor of modern society that we have to face it with stressfully. In the human body, several stress hormones are released by the endocrine glands to keep the internal homeostasis in balance as much as possible during stress. These hormones are designed to face stressful situations by increasing our blood pressure, blood sugar and heart rate. Since the stress has become a part of our daily life the study of stress related hormones and diseases are relevant to the present context [1].

Mainly these stress hormones are of two types namely as glucocorticoid cortisol and catecholamines including adrenalin (epinephrine) and noradrenalin (norepinephrine). As a result of stress the body changes the level of different stress hormones to overcome the adverse effects of flight or fight mode. It involves the activation of automatic nervous system and adrenal medulla leading to an increased concentration of epinephrine and norepinephrine in blood. However, long term exposure to stress is usually having deleterious consequences developing several endocrine disorders, ailments and diseases in human. Some of them are hypo and hypercortisolism as Addison's disease and

Cushing disease respectively. Adrenal glands not producing enough cortisol may result a life-threatening Adansonian crisis usually characterized by the low blood pressure [2,3]. Similarly, hypercortisolism produces Cushing disease whose sign and symptoms are high blood pressure and sugar with moon or rounded and pinkish-red face, fatty hump around the torso and between the shoulders, and purple scratch marks over the abdomen. Late night salivary cortisol for diagnosis of Cushing syndrome has been reported [4-6].

The stress hormones secreted by the hypothalamus-pituitary-adrenal axis (HPA) is often not bad for human health but good and natural to perceive threats. This is normally increased at times of stress. It increases the body's glucose metabolism, reduces the inflammation and controls the blood pressure. Any kind of physical or mental stress, exercise or even wakeup reacts with the pituitary gland. The pituitary gland sends the signal to adrenal glands to produce the right amount of cortisol in the human body. This is a main glucocorticoid stress hormone released from zona fasciculata layer of the adrenal cortex [7-11].

Salivary cortisol is the most studied endocrinological biomarker of human stress [12]. This is a kind of stress hormone found in human blood, urine and saliva usually responding to stress [13-15]. This is also found in the sweat and hair [16-18]. Human cortisol is produced by the adrenal glands directly releasing into the blood stream to develop blood pressure and heart rate. These adrenal glands are found on top of the each kidney. The release of cortisol is ultimately regulated by the pituitary gland. When a person is under stress a huge amount of cortisol is released in blood and saliva. This is usually hypothecated that producing extremely low or high quantity of cortisol can cause health problems in human [15,19,20].

The human cortisol is a steroidal stress hormone having chemical formula as $C_{21}H_{30}O_5$. The exact pathways of human steroidogenesis to produce stress hormones in the human body are given in figure 1. Similarly, the skeletal formula of human cortisol is also being given in figure 2 [21].

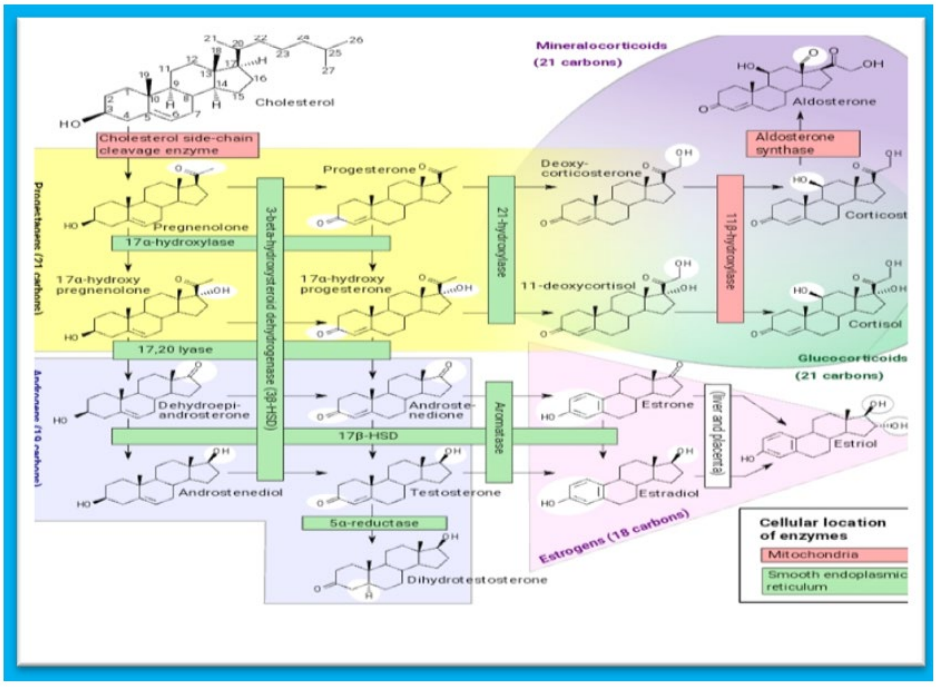


Figure 1: *Diagram of the pathways of human steroidogenesis (Source: Adapted from David Richfield and Mikael Haggstrom 2014).*

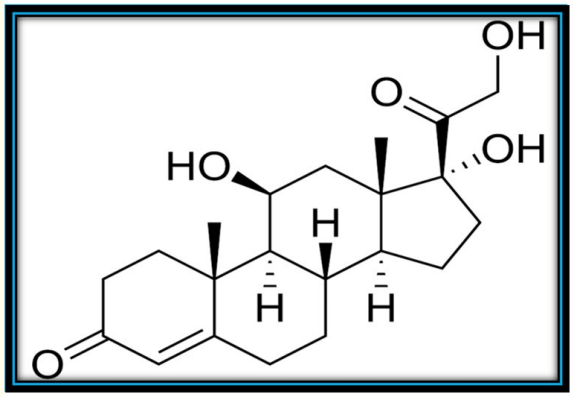


Figure 2: *Structural formula of cortisol.*

The quantity of cortisol found in human is 18 µg/dL. If this is less than < 3 µg/dL, it represents the adrenal insufficiency to produce cortisol. Similarly, this is also observed that the salivary amount of cortisol is much less than the blood. And, this is nearly one tenths than those in serum. According to an estimate, the normal ranges of cortisol found in blood and saliva are 30 to 160 ng/mL and 1 to 1.6 ng/mL respectively [20,22].

Further, several biological and environmental factors like age, sex, populations and circumstances also influence the level of cortisol in blood and saliva. And, the peak concentration is often reached after facing the stressful event within 20 to 30 minutes [23]. Its diurnal circadian normal human profile shows a peak level in the morning after awakening within 30 minutes and declining afterwards throughout the day. The concentration is minimum in the evening. This is popularly known as cortisol awakening response (CAR) in human [20]. Sometimes, this is reversely found in some medical conditions where the HPA axis is not working properly. Blunted CAR has always been resulted into the depression and anxiety disorder in human [24-26]. This is better illustrated in figure 3. Similarly, as psychological stress is mainly related to the emotional stress and pressure, the prolonged emotional disturbances may lead to the development of several health problems in human [26].

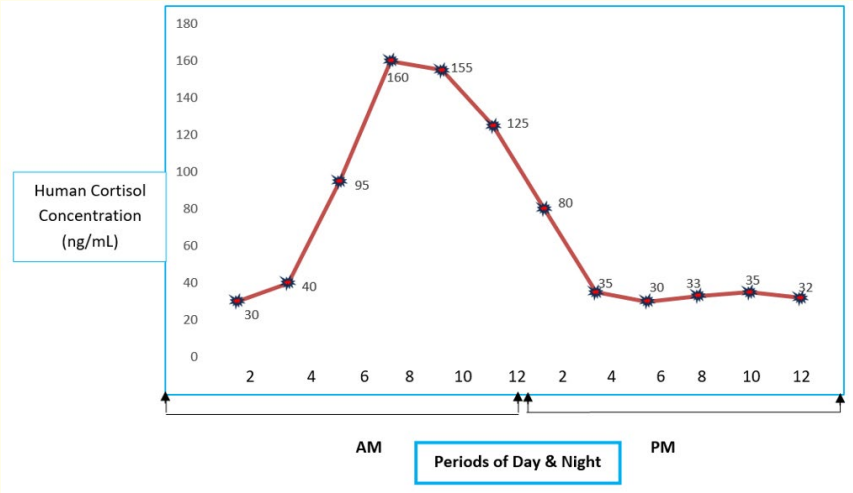
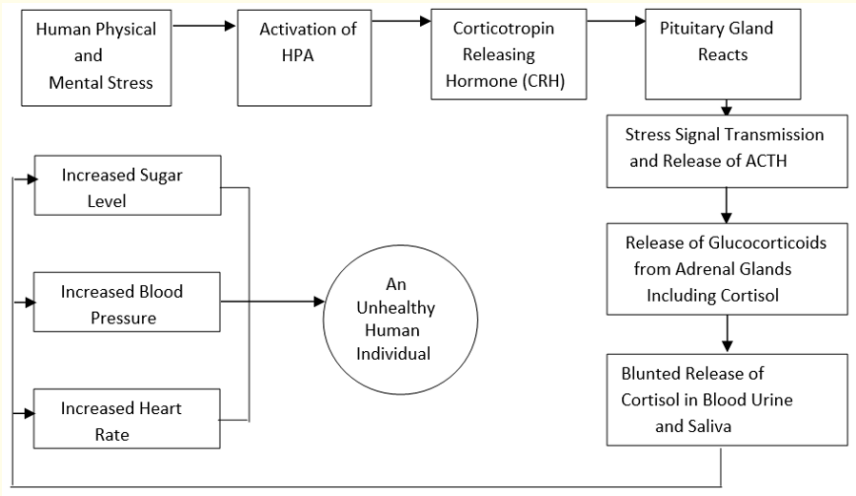


Figure 3: *Diurnal curve of cortisol awakening response in the human body.*

A schematic representation of blunted cortisol production and its consequences in the human body is depicted in flowchart 1. The cortisol if not released properly may cause several ailments and diseases like psychosexual dwarfism [1], depression and mood swings [14], social anxiety disorder [26], obesity and irritable bowel syndrome (IBS) in human [27,28]. Similarly, disturbances in the release of cortisol may also cause some other endocrine disorders like a disturbed release of gonadotropins, vasopressin and insulin and the development of diseases such as gonadal dysfunction, urinary dysfunction and diabetes respectively [10,29].



Flowchart 1: *Schematic representation of blunted cortisol production and their consequences in the human body.*

Stress also increases the production of adrenal cortisol by inhibiting the pituitary secretion of thyroid stimulating hormone TSH leading to the suppression of thyroxin produced by the thyroid gland causing hypothyroidism developing Hashimoto disease in human [30,31]. Similarly, hypocortisolemia may produce hyperthyroidism as Grave's disease [32].

The level of salivary cortisol is altered during the course of human stress. Currently, it has been proved as a powerful and potent biomarker in human in response to stress [33,34]. Salivary lysozyme gives the saliva as antibacterial properties [35]. The level of salivary melatonin is altered during the course of human stress [36]. Similarly, salivary alpha amylase (SAA) increases in response to stress. This is lowest in the early morning and highest in late afternoon [37].

Further, chromogranin A (C_g A) is another salivary biomarker found in human saliva which is quite variable under responses to various stresses like during public speaking, driving, sports, exams, computer operations and noise [38-40]. Further, since the salivary glands are reservoirs of the growth factors, the fibroblast growth factor 2 (FGF-2) has been involved in the regulation of fear expression and anxiety disorder. This is negatively correlated with the development of neurodegeneration in human [41].

Cortisol has been involved in maintaining the child inside the womb during the healthy pregnancy and the initiation of child birth in parturition [42]. Similarly, the level of cortisol measured in maternal saliva during pregnancy has been positively correlated with overweight children [43]. Stress also weakens the human immunity by inhibiting the production of immunoglobulins [44]. There is a strong relationship between the perceived stress depression and anxiety with a low level of I_gA [45].

Conclusion

The paper discusses about the stress and the release of several human stress hormones in equilibrium. Some of them are adrenalin, noradrenalin and cortisol. These hormones are finally secreted by the adrenal glands. Stress hormones are releases in humans to combat the adverse situations faced by them. This is quite a normal human response to stress. But, in certain circumstances the release of these hormones are if blunted they cause several ailments, disorders and diseases in human. Some of these diseases are Cushing's syndrome, Adansonian disease, depression and anxiety disorder, obesity, IBS, Hashimoto disease, Grave's disease and psychosexual dysfunction. Further, human salivary cortisol has been reported potent biomarker for stress in human. Last but not the least, cortisol has always been prescribed in the form of hydrocortisone by the physicians as this is having anti-inflammatory effect in humans. Corticosteroids are synthetic cortisols often being prescribed by the physicians. Sometimes, anabolic steroids have also been prescribed. This is to be noted that these prescriptions must be given under strict medical supervision.

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Ethical Clearance

As this is purely a review article, therefore, it does not require any ethical clearance.

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