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Rol Of Cortisol In Cellular Stress

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***ABSTRACT**: "Stress" can be defined as any situation that tends to disturb the balance between a living organism and its environment. Stress reactions are associated with increased secretion of a series of hormones that include glucocorticoids, mainly cortisol. Glucocorticoids promote or reduce the transcription of many genes that alter the mRNA synthesis of mediator proteins of numerous physiological effects. Some effects of cortisol at the cellular level are stimulation of gluconeogeny, decrease in cellular glucose utilization, increase in blood glucose, adrenal diabetes, increase in liver and plasma proteins, decrease in the transport of amino acids to extrahepatic cells, stimulation of transport to hepatocytes, mobilization of fatty acids, obesity induced by excess cortisol, impeding inflammation by stabilizing lysosomes and blocking the inflammatory response to allergic reactions, all these actions contribute to the organism keep your homeostasis.*
***KEYWORDS:** Stress, homeostasis, cortisol.*

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I. INTRODUCTION

"Stress" can be defined as any situation that tends to disturb the balance between a living organism and its environment. In everyday life there are many stressful situations such as work pressure stress, exams in students, psychosocial stress and physical stress due to trauma, surgery and various medical disorders. Stress reactions are associated with a greater secretion of a series of hormones that include glucocorticoids (cortisol, catecholamine, growth hormone and prolactin), whose effect is to increase the mobilization of energy sources and adapt the individual to their new circumstances [1]; in addition, it has different direct and indirect physiological effects that mediate the response to stress, intensifying the action of other stress hormones or as a suppressor of other components of the system. In this sense, cortisol acts not only as a mediator of the stress response, but as an inhibitor, so that there is no excessive activation of the response [2]; the direct effects of cortisol are, among others, the mobilization of glucose and free fatty acids, a decrease in levels of growth hormones and sex hormones, an increase in cardiac output and blood pressure, among other functions [3]; which try to protect the organism against the effects of a stressful factor and concentrate energy on the recovery of balance in the presence of an acute threat to homeostasis [2]. A strong connection between psychological stress and oxidative stress has been demonstrated, outstanding characteristics of pathophysiological processes in a wide range of disorders or aging [4].

II. MATERIALS AND METHOD

Based on a literature review of different sources like books, the EBSCO database and the open access search engine PubMed, establishing the effects of cortisol on the alteration of cell homeostasis and its relationship with stress.

III. RESULTADOS

Cortisol Production

The synthesis of cortisol begins with the stimulation of the hypothalamic-pituitary-adrenal axis (HPA) which is highly sensitive and easily activated by several stressors. The axis responds by releasing corticotropin-releasing hormone (CRH) from the hypothalamus and the circulating adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland [5]. ACTH acts on the fasciculated area of the adrenal cortex causing glucocorticoid release primarily cortisol [5] [6]. The main effect of ACTH on corticosuprarenal cells is the activation of cell membrane adenylate cyclase, which, in turn, induces the formation of cyclic adenosine

monophosphate (cAMP) in the cytoplasm; the maximum effect is reached at 3 minutes, cAMP activates intra-cellular enzymes that synthesize adrenal corticosteroid hormones (Figure 1) [7].

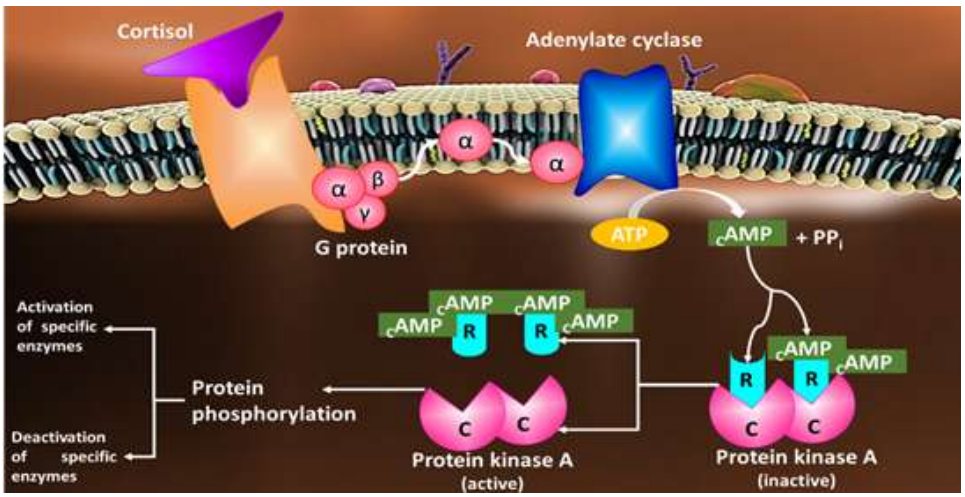

Figure 1. The second adenylate cyclase-cAMP messenger system. The hormone binds to its receptor in the plasma membrane of the white cell. This causes the dissociation of G proteins, which allows the free α (alpha) subunit to activate adenylate cyclase. This enzyme catalyzes the production of cAMP, which eliminates the protein kinase regulatory subunit. Protein kinase phosphorylates other proteins by activating or deactivating specific enzymes and, thus, produces hormonal effects on the white cell (DelgadoSifuentes., 2019).

ACTH stimulates the synthesis of adrenal steroids, increases the number of low-density lipoprotein (LDL) receptors in the corticosuprarenal cell and the activity of the cholesterol-releasing enzyme from LDL. When cholesterol enters the cell, it passes into the mitochondria, where it is cleaved by the action of the enzyme cholesterol desmolase to form pregnenolone (Figure 2) [7].

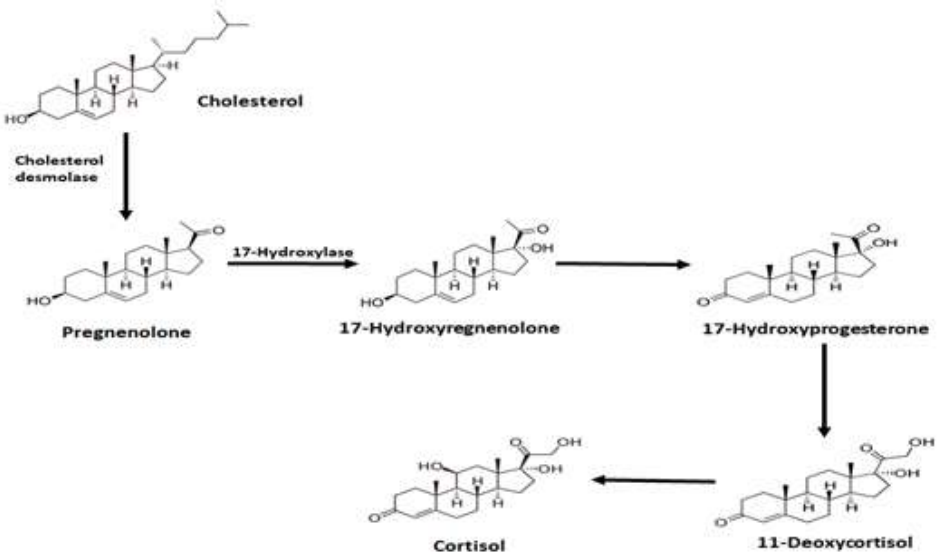

Figure 2. Stages of cortisol synthesis. Cholesterol is transformed into pregnenolone by the action of the enzyme cholesterol-desmolase, which is the limiting step in the suprarenal steroids system, subsequently pregnenolone continues its transformation spends generating cortisol (DelgadoSifuentes, 2019).

Mechanism of action of cortisol

The functions of cortisol in the human body are to control the stress response, blood glucose levels, inflammatory responses and blood pressure. The presence of glucocorticoid receptors in almost every cell in the body, so the cortisol affects many organ systems [8] [9]. This hormone is fat-soluble and easily crosses the cell membrane and interact with receptors located in the cytoplasm [7]. The classic genomic actions of glucocorticoids are mediated by the intracellular glucocorticoid receptor (GR) [10]. In the absence of hormones, GR resides predominantly in the cytoplasm of the cells as part of a large complex of multiple proteins that

includes chaperone proteins (Hsp90, Hsp70 and p23) and inmunophilins (FKBP51 and FKBP52). The multiprotein complex maintains GR in a conformation that favors the binding of high affinity ligands. In the binding ligand, GR undergoes a conformational change, resulting in the dissociation of the multiple protein complex. This leads to a structural reorganization of the GR protein that exposes the 2 nuclear localization signals, and the GR bound to the ligand quickly translocate to the nucleus through the nuclear pores. Once inside the nucleus, GR binds directly to the glucocorticoid response (GRE) elements and stimulates the expression of the target gene. The GRE consensus is a palindromic sequence composed of 2 half sites (GGAACAnnTGTTCT) separated by spacer of 3 nucleotide. GR binds to GRE as a dimer and each half site is occupied by a receptor and, therefore, the spacer of 3 nucleotide between the 2 half sites is strictly necessary for the GR: DNA interaction. The binding of GR to GRE induces conformational changes in GR that lead to the coordinated recruitment of corregulatory and chromatin remodeling complexes that influence the activity of RNA polymerase II and activates gene transcription and repression (Figure 3). A recent study identified a negative element that responds to glucocorticoids (nGRE) that mediates repression of the glucocorticoid-dependent target genes by recruiting corepressors (NCoR1 and SMRT) and histone deacetylases (HDAC). The nGRE consensus is palindromic (CTCC (n) 0-2GGAGA), but differs from the classic GRE in having a variable spacer that ranges between 0-2 nucleotides and is occupied by 2 GR monomers [11].

Glucocorticoid-inducedgeneticexpressionisoftencelltypespecific and only a smallproportionof genes that are activatedbetweendifferenttissues. It has beenshownthattissuespecific target gene activationbyglucocorticoidsdependsontheaccessibilityofthe GR bindingsite, which in turnisdeterminedby DNA methylation and higherorderchromatinstructuressuch as chromatincircuitslongrange. Therefore, tissuespecific target gene activation can be determinedbytissuespecificchromatinlandscape, whichinfluencesthebindingof GR torelated DNA elements. [11].

Transcriptionalregulationby GR isalsomodulatedbytherecruitmentofcoactivators, whichmediatepost-translationalhistonemodifications (acetylation and methylation). Thispropertyhelps alter chromatinstructure and recruitothercofactors, makingchromatin more accessiblefortheassemblyof general transcriptionfactors and the RNA polymerasecomplex in thepromoterofthe target gene. Someofthewell-studied GR corregulators are the SRC familyproteins, the mediator complex and the SWI / SNF, NCoR1 and SMRT complexes. Rapid actions of non-genomicglucocorticoids are mediatedbyphysiochemicalinteractionswithcytosolic GR ormembranebound GR. Unlikegenomiceffects, the non-genomiceffectsofglucocorticoids do notrequireproteinsynthesis, and occursecondsto minutes after GR activation. [11].

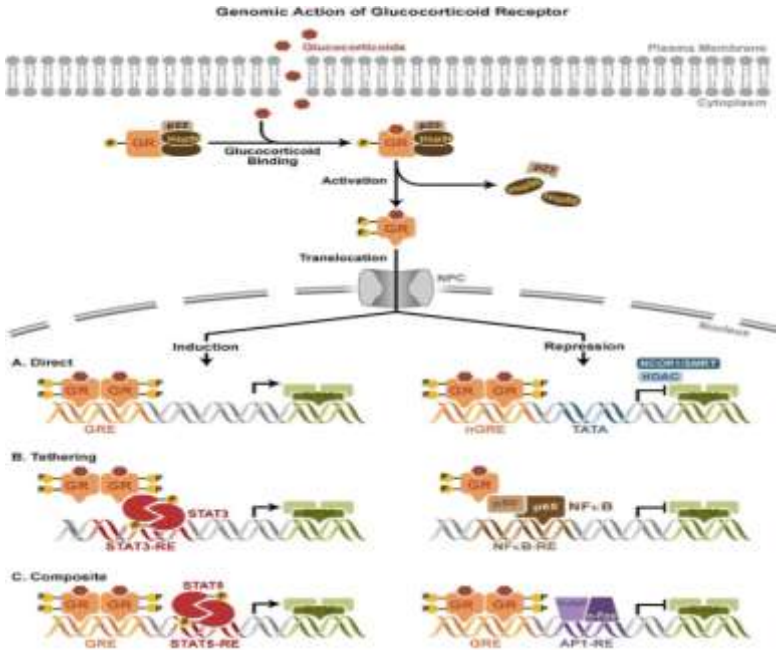

Figure 3. Genomicactionof GR. Uponjoiningtheglucocorticoids, thecytoplasmic GR undergoes a change in conformation (activation), hyperphosphorylates (P), dissociatesfromthemultipleproteincomplex and translocatestothenucleus, whereitregulates gene expression. GR activatesorrepressestranscriptionof target genes bydirect GRE binding, bindingtoothertranscriptionfactorsapartfrom DNA binding, or in a mannercomposedofdirect GRE binding and interactionswithtranscriptionfactorslinkedtoneighboringsites. NPC =

nuclear porecomplex; BTM = basal transcriptionmachinery; TBP = TATA bindingprotein; nGRE = GRE negative; RE = answerelement. [11].

Cortisol effects

Glucocorticoidspromoteor reduce thetranscriptionofmany genes that alter the mRNA synthesisof mediator proteinsofnumerousphysiologicaleffects. Cortisol has bothmetabolic and anti-inflammatoryeffects. Theeffectsoncarbohydratemetabolisminclude: stimulationofgluconeogeny in theliver; therhythmrises, often, between 6 and 10 times. Thiseffectisdue, aboveall, totwofactors; Thefirstevent at the time when cortisol increasestheenzymesthattransform amino acidsintoglucosewithinhepatocytes, thesecondwhen cortisol mobilizes amino acidsfromextrahepatictissues, especiallymuscles. Oneoftheeffectsofincreasedgluconeogenesisis a markedincrease in glycogendeposition in hepatocytes. Thiseffectof cortisol allowsotherglycolytic hormones, such as adrenaline and glucagon, tomobilizeglucoseduringperiodsofneed, as happensbetweenmeals. The basis oftheproposedmechanismsfound in theobservationthatglucocorticoidsdecreasetheoxidationofnicotinamideadeninedinucleotide (NADH) toform NAD+. Since NADH mustoxidizetoallowglycolysis, thiseffectmayexplainthelowercellularutilizationofsugar [7].

Theincrease in glucoseconcentrationstimulatesinsulinsecretion. However, theelevationof plasma insulinvalues isnot as effective in maintaining plasma glucose as in normal conditions [7]. Forreasonsthat are stillpoorlyknown, highglucocorticoidlevels reduce thesensitivityofmanytissues, particularlyskeletalmuscle and adiposetissue, tothe beneficial effectsofglucoseuptake and use characteristicofinsulin[7] [12].

Onepossibleexplanationisthathighconcentrationsoffattyacids, causedbythelipidmobilizingeffectoftheirdepositsbyglucocorticoids, could alter theactionsofinsulinontissues. Consequently, excessglucocorticoidsecretionwould cause abnormalitiesofcarbohydratemetabolism, very similar tothoseobserved in patientswithexcessgrowth hormone. Theincrease in bloodglucosesometimesreachesa proportion (50% or more overthe normal limit) that a stateknown as adrenal diabetes. Oneofthemaineffectsof cortisol onthebody'smetabolicsystemsisthedecrease in proteindepositsofvirtuallyallofthebody'scells, withtheexceptionofthose in theliver. Thisduetothedecrease in synthesis, as well as to a greatercatabolismoftheproteinsalreadyexistingwithinthecells. Botheffectscould be attributedtoreducedtransportof amino acidstoextrahepatictissues. Whenthereis a largeexcessof cortisol, themusclemayweaken, theimmunefunctionsofthelymphatictissuefallto a smallfractionof normal. Cortisol stimulatestheproductionofproteins in theliver, plasma proteins (formedbytheliver and releasedintotheblood) increase; therefore, cortisol mobilizes amino acidsfromextrahepatictissues and, throughthismechanism, depletestissuedepositsofproteins. Theincrease in the plasma concentrationof amino acids and thegreatertransportofthemtohepatocytesby cortisol wouldexplain, thegreater use of amino acidsbytheliver[7]. As a consequenceoftheeffectsonproteinmetabolism, anenzymaticalterationisgenerated in thecell [13]. Manyoftheeffectsof cortisol onthebody'smetabolicsystems are essentiallyduetocortisol'sabilitytomobilize amino acidsfromperipheraltissues and, at thesame time, increaseliverenzymes[7].

Cortisol mobilizesfattyacidsfromadiposetissue, theincreaseofthese in plasma causes their use forenergypurposes; exerting a directeffectthatenhancestheoxidationoffattyacidsinsidethecell. Theabovemay be duetoreducedglucosetransporttoadipocytes[7]. As a resultof cortisol thereis a moderatemobilizationoffattyacids in adiposetissue; People withexcessive cortisol secretiondevelop a peculiar obesity: theexcessfatisdeposited in thechest and head causingthe "buffaloneck" and the round face "full moon." Cortisol isimportanttoresist stress and inflammation, virtuallyanytypeof stress, whetherphysicalorneurogenic, causes animmediate and noticeableincrease in ACTH secretionbytheadenohypophysis, followed a few minutes after a considerable secretionof cortisol bythe adrenal cortex (figure 4) [7].

Sometypesof stress thatincrease cortisol release are: trauma; intense infection, heatorcold, injectionofnorepinephrine and othersympathomimetics, surgery, injectionofnecrotizingsubstancesunderthe skin, immobilization and debilitatingdiseasesofalmostanytype. In highconcentrationsthis hormone has anti-inflammatoryeffects[7], becauseitsignificantlysuppressestheproductionofprostaglandin E2 (PGE2) and decreasestheexpressionof genes and proteinsof inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) in a dosedependentmanner. In addition, cortisol inhibits mRNA expressionofproinflammatorycytokines, including tumor necrosis factor alpha (TNFα), interleukin-1β (IL-1β) and interleukin-6 (IL-6) [14]. Theadministrationoflargeamountsof cortisol allowsto block inflammationoreven reverse manyofitseffects, once initiated. Cortisol blocks theinflammatory response toallergicreactions, butdoesnotinfluencethebasicallergicreactionbetweentheantigen and theantibody. Cortisol reduces thenumberofeosinophils and bloodlymphocytes; Thiseffectbeginswithin a few minutes oftheinjectionofthe hormone and isaccentuated after a fewhours. Thedetectionoflymphocytopeniaor eosinopenia constitutesanimportantdiagnosticcriterionof cortisol hyperproductionbythe adrenal gland[7],

excessglucocorticoids cause central obesity, type 2 diabetes, hypertension and other cardiovascular riskfactors[15] [16] [17].

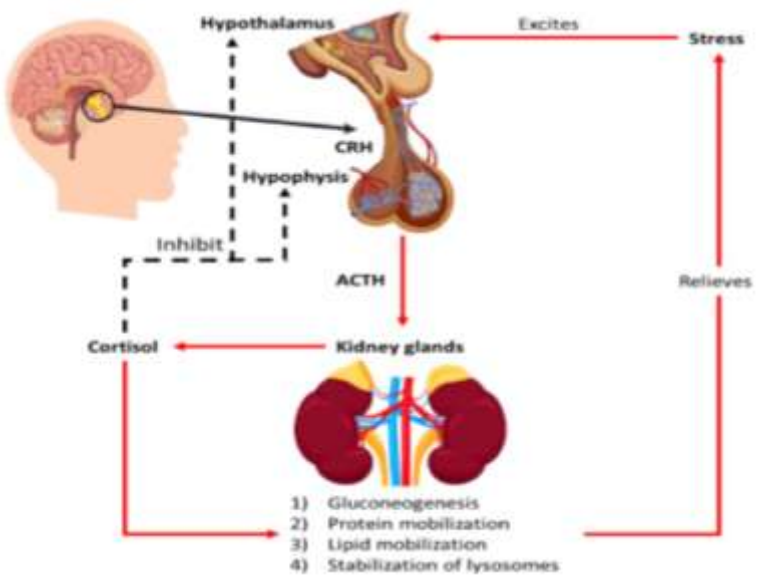

Figure 4. Cortisol production, regulation and effectsaimed at relieving stress processes. Stressors, whetherphysicalor mental, excite thehypothalamus, whichrespondsbyreleasing CRH, whichpromotesthereleaseof ACTH bytheadenohypophysis, resulting in anincrease in theconcentrationof cortisol thatpromotesgluconeogenesis, proteinmobilization, mobilizationoflipids and anti-inflammatoryeffectsbylysosomestabilization (Delgado, B., 2019).

Relationship of cortisol with stress

The stress response is a normal coordinated physiological system whose function is to increase the probability of survival, but also designed to be an acute response: it turns on when it is necessary to return the organism to a stable state and turns off when homeostasis is restored [2] The HPA axis is modulated at different levels during stress [18]. The burden of chronic stress and the accompanying changes in personal behaviors (smoking, eating too much, drinking, poor quality sleep; also known as "Lifestyle") is called allostatic overload [19]. The stress response occurs in the central nervous system (CNS), it depends on the communication between the neuronal pathways of the cerebral cortex, the limbic system, the thalamus, the hypothalamus, the pituitary gland and the activating reticular system [2].

Glucocorticoids, which regulate metabolism and stress resistance, are cortisol (hydrocortisone), corticosterone and cortisone. Of these 3 hormones secreted by the fasciculated area, cortisol is the most abundant, and is attributed to about 95% of glucocorticoid activity [2]. The control of glucocorticoid secretion occurs through a negative feedback system [6].

Some organisms may cope with stress stimuli, while in others, repeated daily stress could lead to neuroendocrine coping mechanism disorder, producing a wide range of harmful effects at the physiological level and psychological homeostasis [5]. Physical and mental health is damaged by the chronicity of the response. Stressors assume different patterns in relation to time. The frequency or chronicity of the circumstances to which the body must respond often determines the availability and efficiency of stress responses. Chronic exposure to a factor that generates stress can induce system fatigue and compromise its effectiveness. Acute stress reactions are those that are related to the autonomic nervous system (ANS), in response to fight or flight [2].

Chronicity and excessive activation of the stress response can result from chronic diseases and also contribute to the development of long-term health problems. Chronic activation of the stress response is an important public health problem both from the perspective of health and its costs [2]. Stress is linked to countless physiological disorders, such as diseases of the cardiovascular, gastrointestinal, immune and neurological systems [20]; also with psycho-emotional disorders such as depression, chronic alcoholism, excessive drug use, eating disorders, accidents and suicide [2].

Relationship of cortisol with oxidative stress

Chronic exposure to stress promotes oxidative damage through frequent and sustained activation of the hypothalamic-pituitary-adrenal axis [21]. Stress hormones can affect the production of reactive chemical species

and antioxidant status, people with different coping styles may also differ in the oxidative state [22]. Oxidative damage is caused by reactive oxygen species (ROS) [21], which are highly harmful and reduced forms of oxygen, which includes the superoxide anion O_2, hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH) not mitigated by antioxidants. Under healthy conditions, ROS production is primarily a byproduct of daily mitochondrial respiration that fuels the metabolism of basic processes. Oxidative stress reflects a state of cellular imbalance, in which the production of ROS exceeds antioxidant mechanisms that neutralize ROS [23] [21], resulting in harmful effects nearby molecules, such as DNA, RNA and lipids [24]. Reactive oxygen species are produced by all aerobic cells and play an important role in aging, as well as in age-related diseases [25]. Therefore, dysfunctional mitochondria can promote oxidative stress [26]. Cortisol has an inverted U-shaped relationship with mitochondrial function [21].

Mechanism of adaptation to stress

The ability to adapt to a wide variety of environments and stressors is not unique to humans. Living organisms, no matter how primitive they are, do not passively submit to the impact of environmental forces. They try to respond adaptively, each with their own and most appropriate way [2]. Energy is required to sustain life and allow adaptation to stress. At the cellular level, energy is largely derived from mitochondria. Four main elements connect mitochondria with stress: (a) energy is required at the molecular level, epigenetic, cellular, organelle and systemic to sustain the stress response components; (b) glucocorticoids and other steroid hormones are produced and metabolized by mitochondria; (c) reciprocally, mitochondria respond to neuroendocrine and metabolic stress mediators; and (d) experimentally manipulate mitochondrial functions alters physiological and behavioral responses to psychological stress. Therefore, mitochondria are endocrine organelles that provide energy and signals that allow a direct adaptation to stress. Without energy, adaptation to stress is not possible and the body dies [26]. The mechanisms with more complex evolution are the social responses by which people or groups modify their environments, their habits or both, with the aim of achieving a way of life that is more appropriate to meet their needs. Humans, due to the effect of their nervous system and intellect so developed, often have alternative mechanisms for adaptation and have the ability to control many aspects of their environment [2]. Adaptation implies that an individual has successfully generated a new balance between the stressor and the ability to face it. The coping mechanisms are emotional and behavioral responses that are used to control the threats to the physiological and psychological homeostasis of the human [2]. The main stress hormones are epinephrine and glucocorticoids, which have critical functions in the stress adaptation process. The fight or flight response involves the activation of the sympathetic nervous system, which leads to the rapid release of epinephrine from the chromaffin cells. The synthesis and release of cortisol comprises the second phase of the neuroendocrine response, which has a long-term effect on adaptation to stress [27].

Adaptation is more efficient when changes occur gradually and not suddenly. Time, genetics, age, health status, nutrition, sleep-wake cycles, strength and psychosocial factors, influence a person's appreciation of a stress factor and the coping mechanisms used to adapt to the new situation [2]. The ability to adapt decreases at the extremes of age and sex; Sex-based differences in the activation of the stress response may partly explain differences in susceptibility to diseases in which the stress response could play an etiological role [2]. At baseline, the man secretes more ACTH than the woman, but in the periphery cortisol levels are identical, suggesting an increase in the sensitivity of corticosuprarenal to ACTH in women [28].

Sleep is considered a recovery function in which energy is restored and tissues regenerate. It has been shown that sleep disorders and sleep-wake cycle disorders alter immune function, the normal circadian pattern of hormonal secretion and physical and psychological performance. Rest and activity, work and leisure time, and the consumption of food and beverages, play an important role in adaptation to stress, in the development of disease and in the response to medical treatment. In some people stress can cause sleep disorders and in others sleep disorders can lead to stress [2]. Early life events influence patterns of emotional response and stress throughout life and alter the rate of brain and body aging [29].

The scientific interest in the social environment as a cause of stress has gradually expanded to include the social environment as a source that modulates the relationship between stress and health. It can be presumed that people capable of mobilizing strong sources of support from their social relationships are more able to withstand the negative effects of stress on their health. Close relationships with other people can have positive effects and also have the potential to generate conflict, and in some situations they can make the person less skilled in dealing with the stressors of life [2].

IV. CONCLUSION

Stress reflects a state of cellular imbalance, as a consequence of the activation of the hypothalamus-adenohypophysis-adrenal glands axis, which is highly excitable by stressors either physical or psychological, inducing a rapid release of cortisol that, in turn, triggers a set of metabolic effects aimed at reducing the harmful

nature of stress and maintaining cellular homeostasis, however the response to stress is influenced by a variety of factors ranging from the strength of the individual to psychosocial factors.

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