IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

STRESS:A RECIPE FOR ACCELERATED AGINNG

SULAGNA CHAKRABARTI

ASSISTANT PROFESSOR

SEACOM B ED COLLEGE

❖ INTRODUCTION:-

The word stress is derived from Latin word "stringere" or tightness. Researchers view stress as the physiological and psychological condition that a person experiences when a situation is perceived as threatening harmful or demanding.

There are two types of stress -acute and chronic. Acute stress is stress resulting from specific events or situations that involves novelty, unpredictability, a threat to the ego, and leaves us with a poor sense of control. This ‘on the spot' type of stress can be good for us because the stress hormones released help our mind and body to deal with the situation.

Chronic stress is the response to emotional pressure suffered for a prolonged period over which an individual perceives he or she has no control. It involves an endocrine system response in which occurs a release of corticosteroids. While the immediate effects of stress hormones are beneficial in a particular situation, long term exposure to stress creates a high level of these hormones that remains constant. This may lead to high blood pressure, damage to muscle tissue, inhibition of growth, suppression of the immune system, and damage to mental health. Aging is the process of getting older. It represents the accumulation of changes in an animal over time encompassing its physiological, psychological and social changes. In fact chronic stress has been linked to heart disease, high blood pressure, high cholesterol, type two diabetes, and depression. But the effects of stress are worst for people at risk for developing these and other problems. For instance, if one has a family history of heart disease, diabetes, high blood pressure or has unhealthy lifestyle habits, then chronic stress can flip the switch that turns on these health problems.

As chronic stress is more harmful than acute stress so I discuss in this project that "How Chronic Stress Accelerated Aging".

Chronic stress is the response to emotional pressure suffered for a prolonged period over which an individual perceives he or she has no control. It involves an endocrine system response in which occurs a release of corticosteroids.

While the immediate effects of stress hormones are beneficial in a particular situation, long term exposure to stress creates a high level of these hormones that remains constant. This may lead to high blood pressure, damage to muscle tissue, inhibition of growth, suppression of the immune system, and damage to mental health.

Aging is the process of getting older. It represents the accumulation of changes in an animal over time encompassing its physiological, psychological and social changes. Chronic stress can effect human health through a myriad of behavioral and biochemical pathways. Chronic stress induces anabolic and catabolic imbalance -characterized in part by high cortisol, glucose, insulin, and low androgens and growth hormones may lead to oxidative stress and systemic inflammation, which in turn impair cell aging processes. Consumption of energy-dense food and obesity also play a key mediating role in this pathway. Our modern Lifestyle drives us to consume calorically dense food during times of stress. Both chronic stress arousal and overeating can cause insulin resistance and they together promote energy storage in abdominal fat tissue. These body habitués is associated with systemic inflammation and oxidative stress which in turn affects cell metabolism and can accelerated cellular aging, possibly affecting autophagy, sirtuins, and telomere maintenance. Chronic stress induces biochemical imbalance, the direct central effects and indirect effects from adiposity, promote leukocyte cellular aging. Cell aging is just one of many outcomes of stress, and likewise stress is just one of many factors affecting cell aging.

Figure 1:- CAUSES OF STRESS

❖ AIMS AND OBJECTIVES:-

In modern society, we are faced with excessive psychological stress, as well as an epidemic of overeating, and the two together appear to have synergistic effect. Chronic stress can lead to overeating, co-elevation of cortisol and insulin, and suppression of certain anabolic hormones. This state of metabolic stress in turn promotes abdominal adiposity. Both the direct stress response and the accumulation of visceral fat can promote a milieu of systemic inflammation and oxidative stress. This biochemical

environment appears to be conductive to several cells aging mechanism, mainly dampening telomerase and leading to telomere length shortening and earlier mortality. In this way, chronic stress may influence a variety of diseases through a biochemical cascade leading to immune cell senescence. Certain psychological temperaments at high risk of this stress cascade (mainly anxiety prone) , gene-environment interactions, and potential interaction for interrupting the stress-aging cascade are discussed in this project.

As we lead a stress full life so the burden of diseases of aging on the healthcare system will likely to be overwhelmed, it is important to gain a deeper understanding of biological aging. The development of age related diseases occurs at different rates in individuals, and psychological distress appears to be an important factor promoting earlier onset of age related diseases. The aim of this projects to aware the people about 'how chronic stress accelerated aging 'and also to improve public health.

➢ METABOLIC MECHANISM OF AGING: -

Chronic stress plays an important role in the metabolism of aging. The figure 1demonstrate how a stress induced anabolic /catabolic hormone imbalance - characterized by high glucose, cortisol, and insulin and low androgen and growth hormones – may lead to oxidative stress and systemic inflation, which in turn impair cell aging process.

❖ AGING, ALLOSTASIS, AND BIOCHEMICAL STRESSORS:-

Allostasis appears to be at the nexus between stress and aging. Allostasis describes how our normal regulatory physiological systems fluctuate within rather large operating ranges to match environmental demands. Allostasis creates ‘stability through change’ by changing our level of arousal to meet the current demands.

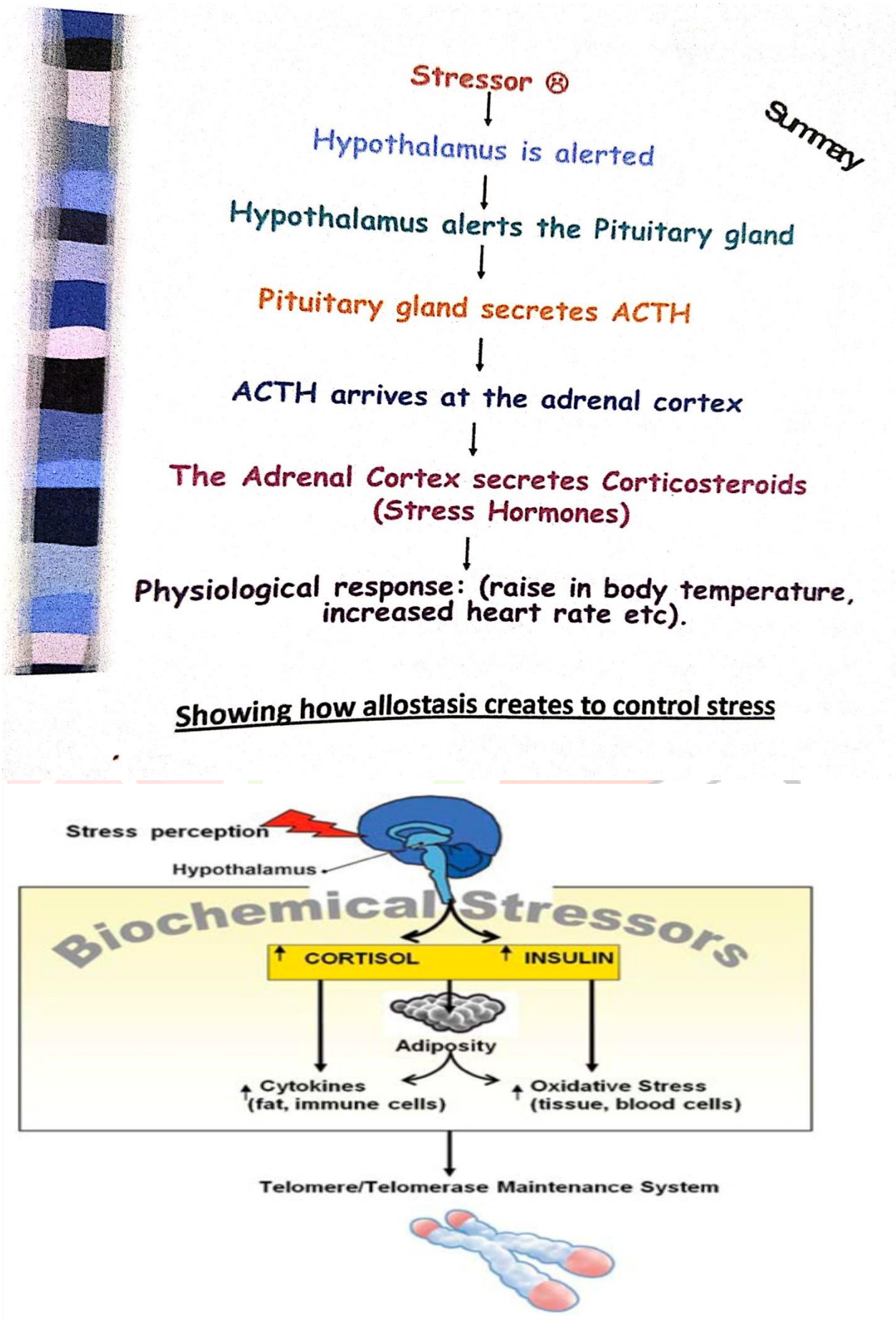


FIGURE 2:- SOME SYSTEMIC AND CELLULAR EFFECTS OF CHRONIC STRESS

At the systems level, hormones are one of the primary allostatic regulators. At the cellular level there are many mechanisms that regulate the stress responses. Efficient allostasis describe facile adaptation, such as quick peak stress response to mount energy to an acute stressors, and a rapid return to baseline, when the stressor terminates. Impaired allostasis is characterized by exaggerated reactivity peaks and sluggish recovery. Chronological aging impairs an organism's ability to sustain efficient allostasis when responding to different stressors. In human this is well demonstrated by examining physiological regulation such as dynamic Hypothalamic - Pituitary – adrenal (HPA) axis responses. The cortisol response to stressors can be exaggerated in the elderly, and additionally, there is a sluggish negative feedback, so that the elderly, and additionally, there is a sluggish negative feedback, so that cortisol stays elevated longer.

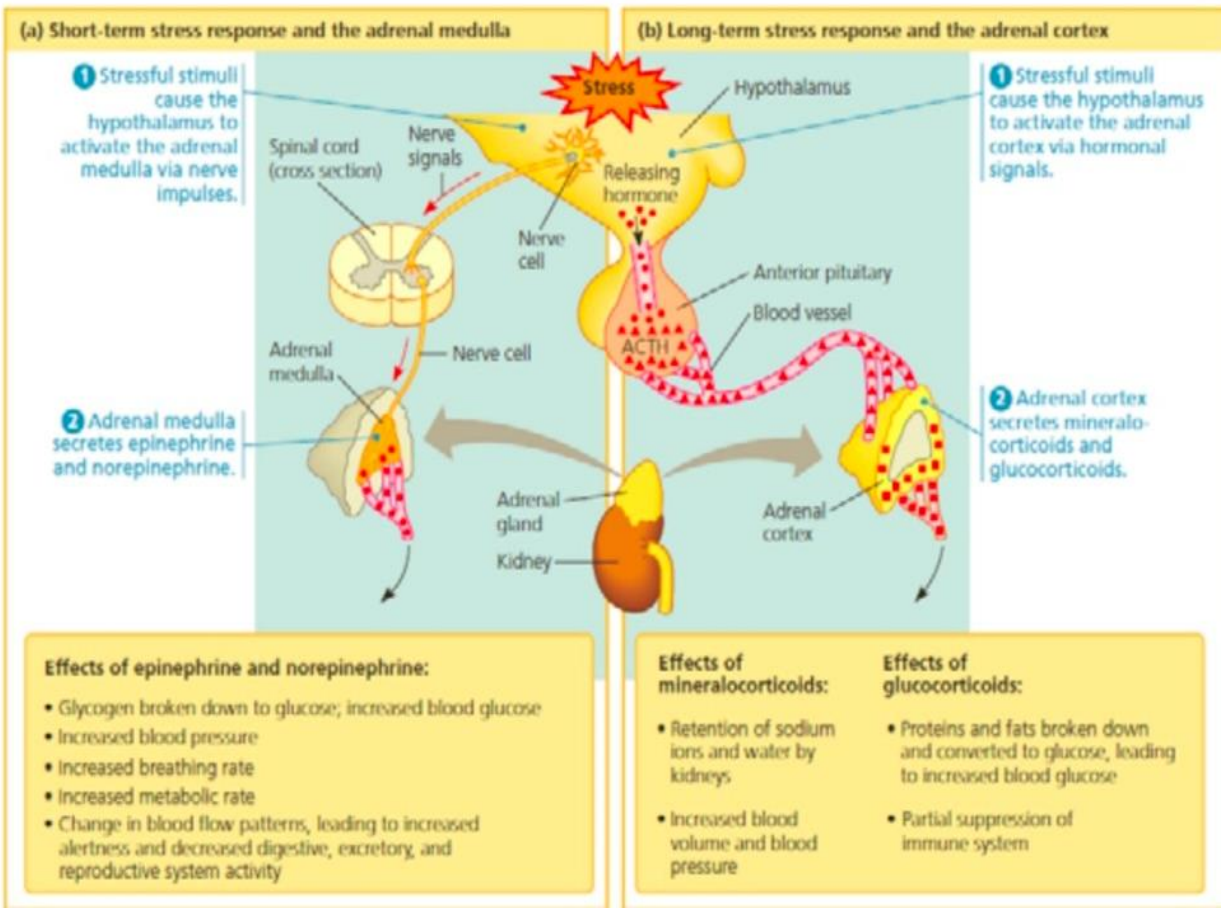


FIGURE 3: SHOWING HORMONES AS PRIMARY ALLOSTATIC REGULATOR

Chronic stress causes certain regulatory system to have altered set points as well as changed response profiles. Aging is also associated with altered set points in multiple regulatory parameters such as cytokines, blood pressure, and lipids, and often deficiencies in androgen and IGF - 1. An index of these markers is commonly used as a way to measure "allostatic load ", the damage

due to repeated fluctuation of the stress response. A high allostatic load index, indicating altered set points, has been linked to earlier mortality. [16, 19]

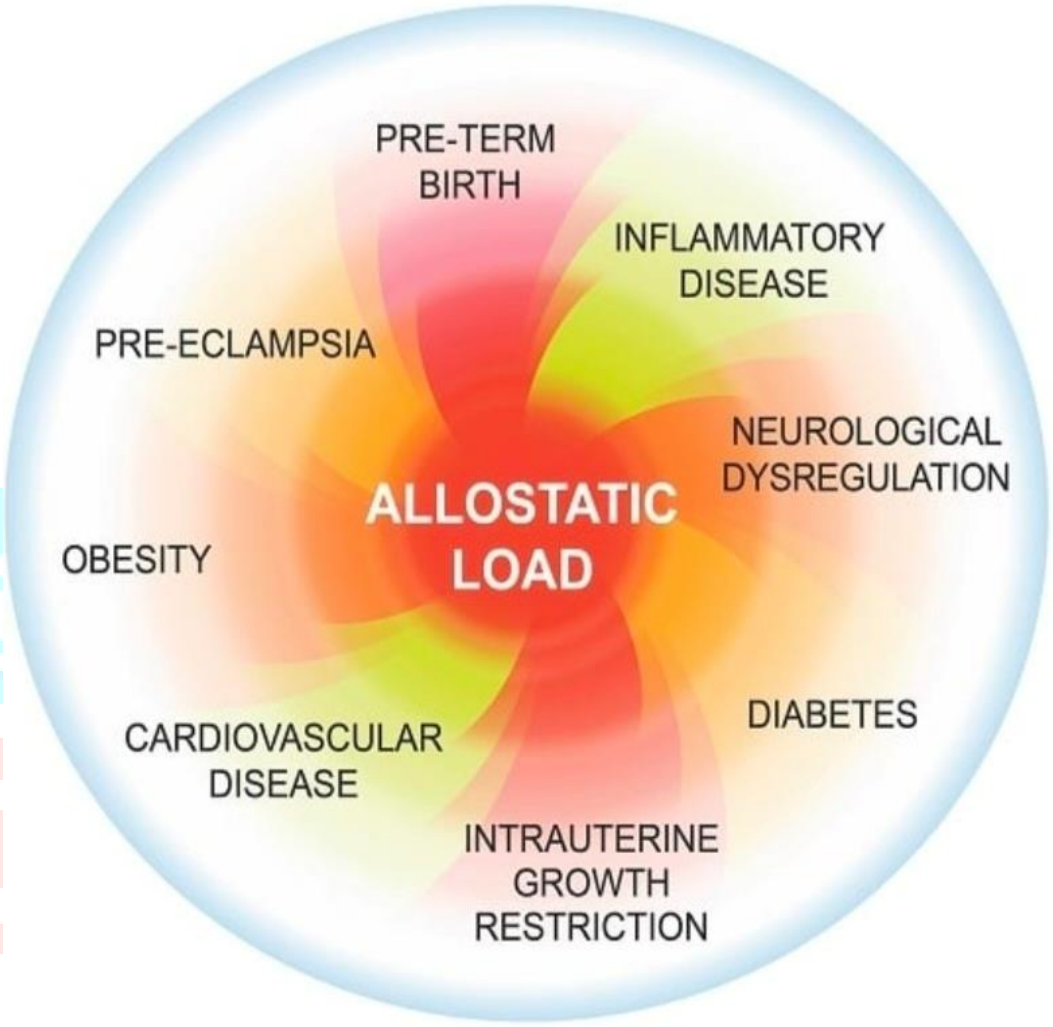


FIGURE 4: SHOWING HARMFUL EFFECT OF ALLOSTATIC LOAD

❖ **ANABOLIC/CATABOLIC HORMONAL IMBALANCE:-**

Chronic stress tends to shift the hormonal balance towards low levels of the anabolic hormones that promote growth of lean and skeletal mass and prevent adiposity, such as androgens and IGF-!. It also can promote greater cortisol levels, or cortisol levels that are not well counter --regulated by anabolic hormones. This has been labeled Anabolic / catabolic imbalance (A/C imbalance) In addition cortisol increases insulin levels. Although insulin is anabolic and under normal basal conditions can increase both lean mass and fat mass, co - elevation of insulin with cortisol preferentially increases abdominal fat stores, making high insulin part of the A/C imbalance profile.

Chronic stress can affect the Hypothalamic – Pituitary - Adrenal axis in many ways. For example, it can lead to the impaired negative feedback of the HPA axis, to slower recovery from stressors, and to either higher or lower cortisol levels. A considerable body of research has linked depression and chronic stress to elevated stress hormones, mainly cortisol and catecholamine, though not in all cases. Chronic stress has also been linked to hypocortisolemia or low Corticotrophin - Releasing hormone (CRH).

Anabolic hormones including Dehydroepiandrosterone(DHEA) and Testosterone and Somatotropic axis , mainly Growth hormone(GH) and Insulin like growth factor 1 (IGF - 1), also play an important role in stress and aging. These hormones decrease with age and are often linked to poor metabolic health. It is notable that androgens appear to have gender Specific effects on disease. Testosterone and in some cases DHEA-S, predict lower incidence of diabetes and metabolic disease in women. Like aging chronic stress can lead to decreased lGF-1, GH, DHEA, and Testosterone levels, although there are exception to this. As described elsewhere, chronic stress and obesity have independent and interactive effects on suppressing these hormones as well as disrupting the gonadal axis and reproductive function.

DHEA often serves as an anti-glucocorticoid and can buffer effects of inflammation and oxidative stress. Therefore, deficits anabolic hormones may in some cases leave action of cortisol unopposed, anabolic hormones at sufficient levels signify restorative process, while deficits may indicate earlier aging and risk of mortality. For example, A/C imbalance is related to cachexia and earlier mortality from chronic heart failure (CHF). Low level of testosterone predicted mortality in male veterans. Another study examined whether low levels of IGF-1, Testosterone, and DHEA were related to early mortality in men, while adjusting for various behavioral factor as well as presence of chronic diseases.

The following table shows anabolic /catabolic hormonal changes in chronic stress.

Potentially damaging mediator	*Potentially protective or restorative mediator*
INCREASED	**DECREASED**
• Hypercortisolemia • Synaptic glutamate • Intracytoplasmic calcium • Free radicals(oxidative stress) • Inflammatory cytokines	• Neurosteroids (DHEA, allopregnenolone) • Insulin sensitivity • Intracellular glucose • Antioxidants • Anti-inflammatory/immunoregulatory cytokines • Neurotrophic factors

GH and lGF-1 decrease with aging, a phenomenon associated with muscle atrophy, but anabolic hormones also promote malignancy such as breast cancer. People with low levels of GH have increased adiposity, insulin resistance, and increased incidence of cardiovascular disease, but nevertheless have very low rates of cancer. Thus, growth factors are double - edged swords: they have favorable effects on musculoskeletal and thus metabolic health, yet increase the risk of cancers. Despite the links between GH/ IGF-1 and good metabolic health in humans, GH / IGF hormones are linked to shorter lifespan in lower species and mammalian modes. New research on genetic variation of genes controlling IGF-1/GH signaling pathway , such as the FOXO gene, support the animal studies showing that mutations in these signaling pathways are inked to longevity in human as well, painting a complex picture of the role of these growth hormones inhuman health.

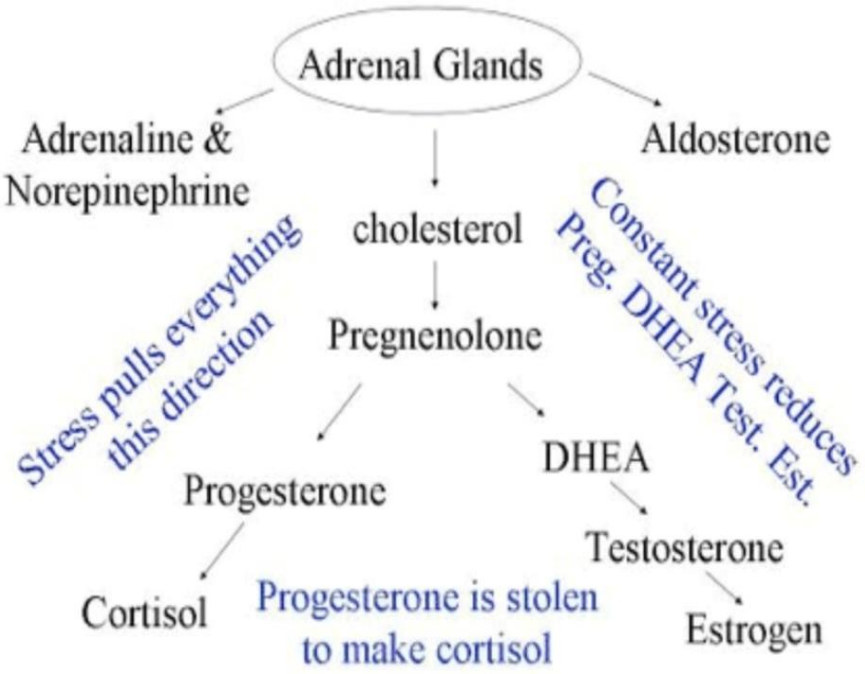


FIGURE 5: SHOWING HORMONAL IMBALANCE DURING STRESS

❖ **GLUCOCORTICOID, CHRONIC STRESS, AND AGING:-**

In stressful state, corticotrophin releasing hormone (CRH) and Arginine Vasopressin (AVP) are released from Para ventricular neurons that project from the Para ventricular nucleus to median eminence. CRH and AVP travel from hypothalamus via the hypophyseal - portal blood vessels to the anterior pituitary gland where they act synergistically via type 1 CRH receptor to trigger release of Adrenocorticotrophic hormone (ACTH) from the corticotrophs into the systemic circulation. In turn, ACTH acts on the adrenal cortex via type 2 melanocortin receptors to initiate the synthesis of glucocorticoids immediately into the systemic circulation in a diffusive manner. On the other hand, the sensitivity of HPA to incoming stimuli is modulated by a GC mediated negative feedback system through which the sequential release of CRH / AVP and ACTH from the hypothalamus and anterior pituitary gland is suppressed.

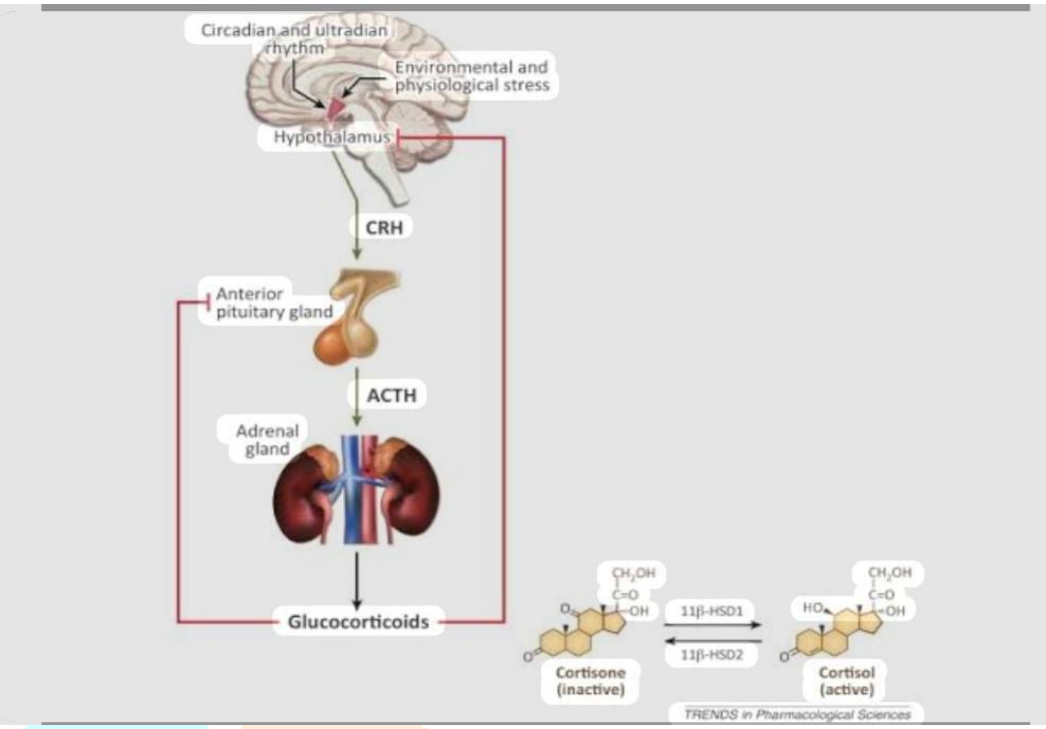
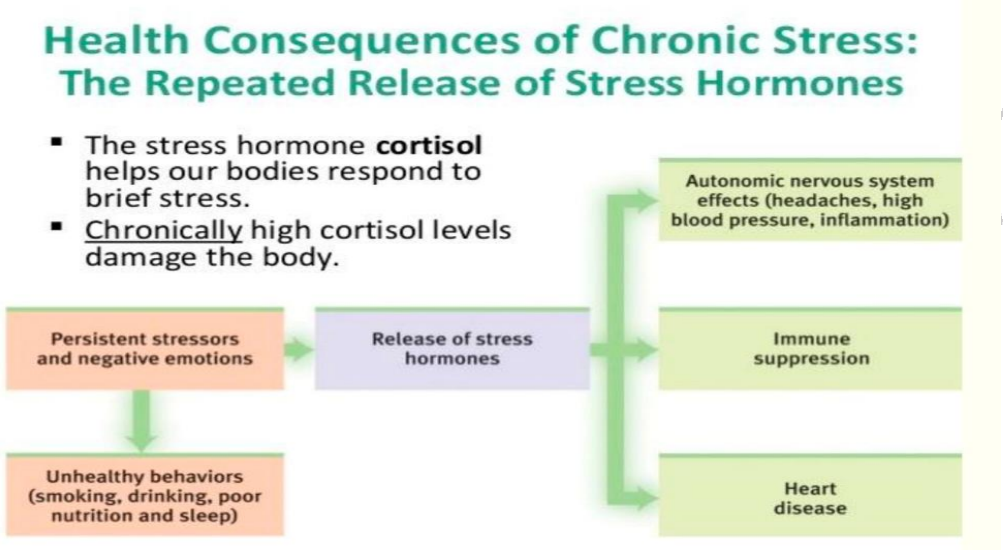
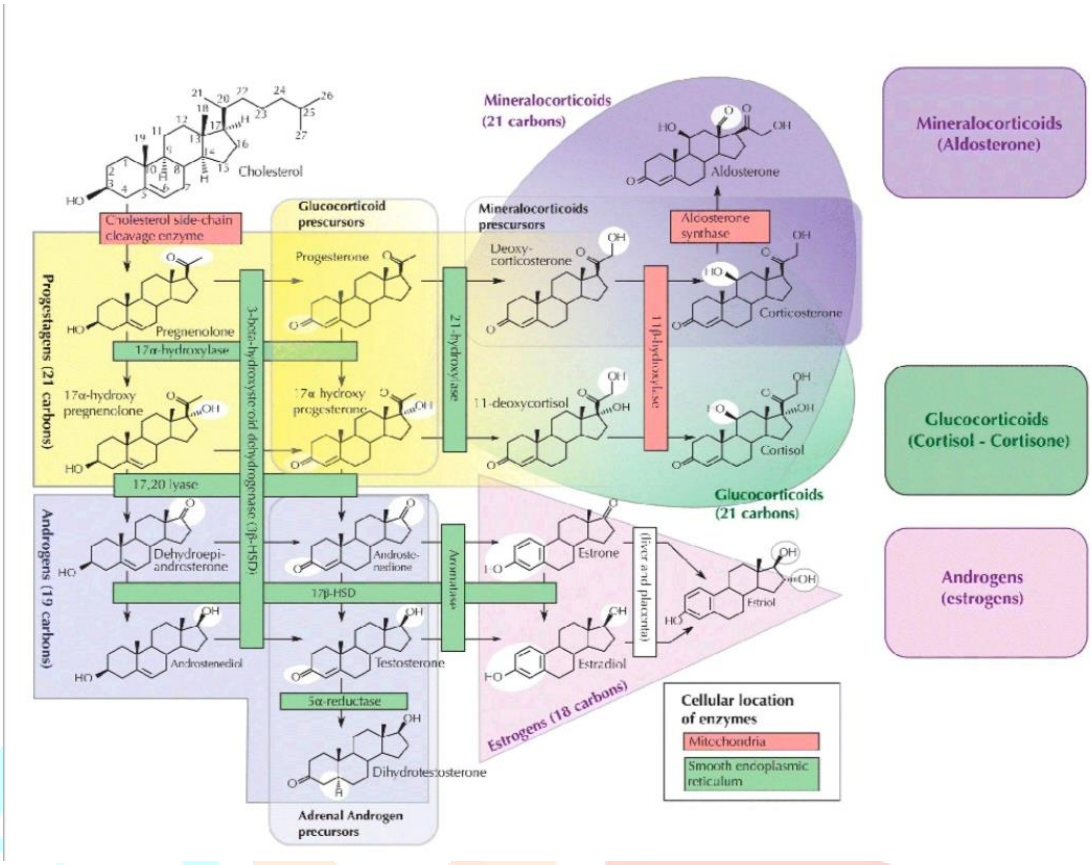


FIGURE 6: THE RELEASE OF GLUCOCORTICOIDS FROM ADRENAL GLAND



Synthesis of glucocorticoid from adrenal gland occurs by the following ways;



❖ NEUROTROPIC MODEL OF STRESS IN CASE OF AGING:-

Chronic stress increases glucocorticoid level which cannot come back to its normal state. The "neurotropic model "of chronic stress posits that diminished hippocampal BDNF (brain derived neurotropic factor), impairs the ability of stem cells in the sub granular zone of the dentate gyrus to proliferate into mature cells that remain viable BDNF is very important because it attenuates glucocorticoids induced neuronal death, and BDNF activity synergizes with telomerase activity in promoting the growth of developing neurons. Excessive glucocorticoids cause hippocampal neuron degeneration by decreasing BDNF activity, so aging is accelerated.

Chronic stress also decreases DHEA (Dehydroepiandrosterone) which serves as an anti-glucocorticoid. So glucocorticoid increases with stress. Glucocorticoids up regulate calcium ion buffer calbindin D28K and high levels of calbindin D28K suppress post-titanic potential. Stress may lead to slower auto phosphorylation of Camkll at thr305.Thr 305 maximizes the binding of calmodulin in the postsynaptic neuron and results in higher level of calcium ion, perhaps potentiating toxicity.

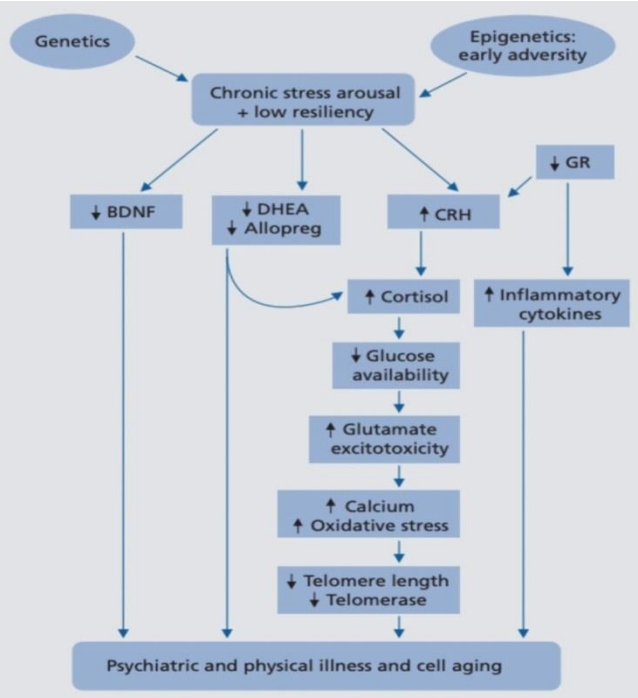


FIGURE 7: THEORETICAL MODEL OF AGING IN CHRONIC STRESS

❖ **SUPPRESSION OF NCAM GENE EXPRESSION BY GLUCOCORTICOID, ACCELERATE AGING**:-

Glucorticoids are lipophilic steroids thus can readily enter the neuron to interact with the intracellular glucocorticoid receptor (GR) results in conformational changes in the GR molecule and induces a poorly understood process known as receptor activation (figure 5). Down regulation of NF-KB-driven NCAM (nuclear cell adhesion molecules) genes result from an interaction between activated GR and p-65 subunit of NF-KB. Direct interaction between p-65 and activated GR modifies or changes in p-65 conformation that masks the activation domain of p-65 which result in down regulation of NCAM gene transcription. In addition, a potential AP-1 recognition sequence is found very close to apparent transcription start site on NCAM genes which also be repressed by GR. The mechanism behind that is GR and AP-1 simply compete for a common co activator complex containing CREB-binding protein (CBP) or p300. But it can only explain the trans repression of AP-1 activity by GR when the amount of CBP/p300 is limited. Activated GR may induce AP-1 to recruit a corepress0or complex instead of co activator.

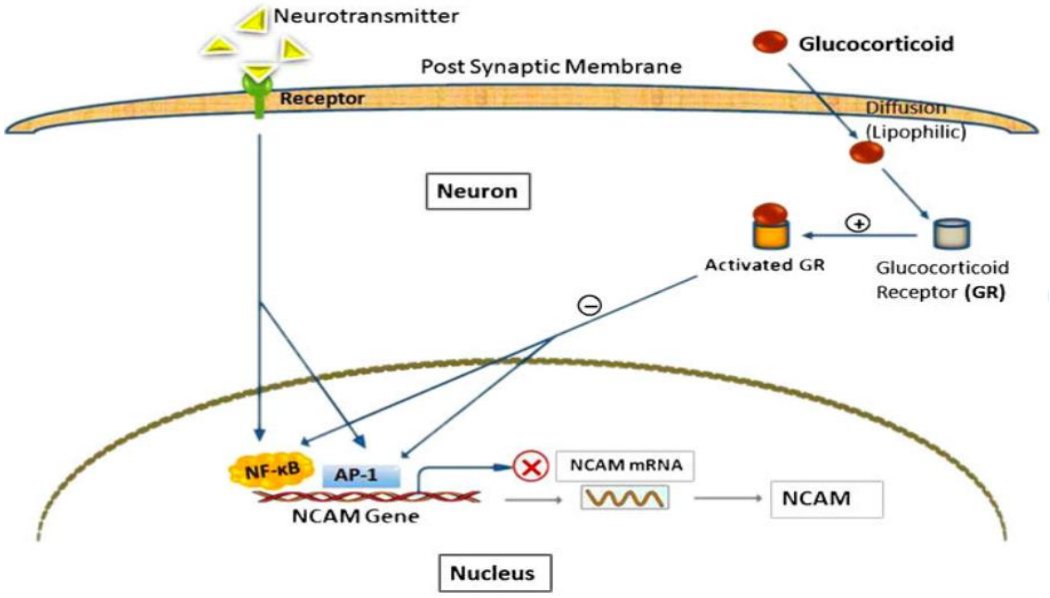


FIGURE 8: SUPPRESSION OF NCAM EXPRESSION BY GCS

NCAM is considered to be a reliable marker of synaptic plasticity. So reduction in NCAM concentration regarded as a consequence of structural changes.

Chronic stress increases the glucocorticoid synthesis, excess glucocorticoid triggers glucocorticoid receptor to its active state which negatively regulated NF-KB and AP-1 and consequently blocking NCAM gene, so there is no synaptic plasticity. Hence aging is accelerated by excess glucocorticoids in chronic stress.

❖ GCS MEDIATED T-CELL RECEPTOR SIGNAL INHIBITION AND ACCELERATION OF AGING:-

:-

Aging is associated with the immune senescence of most molecular machines of immune system like dysregulation of inflammatory processes, impaired wound healing due to diminish ability of macrophage to produce proinflammatory cytokines and decreased ability of T-cells response when challenged with antigen .[1]

Indeed, GCS have direct inhibitory actions on many inflammatory and structural cells involved in inflammation. GCs slow down the release of inflammatory mediators from eosinophil's and mast cell. The inhibitory effect on inflammatory mediator released from mast cell may be linked to the reduction in Interleukin (IL-2) and stem cell factor production. T-cell activation, proliferation, survival, and release of lymphocytes such as IL-2 and macrophage colony stimulating factor, which likely to play an important role in the recruitment and survival of inflammatory cell but are very effectively inhibited by Glucocorticoids. Figure 6 represents mechanism of immune suppression of T-cell activation by GCs. Schematic representation of TCR signaling process subdivided into two sides. The left side presents normal signaling through which IL-2 gene expressed. But on right side it is seen that GR mediated TCR signaling where intracellular membrane signal complex is negatively regulated and consequently the tuned inner

membrane complex loosening their relation results in TCR signal impairment, through this IL-2 gene suppression is retarded. As IL-2 gene suppresses the T-cell and B cell cannot activate, proliferate and act against specific antigen, the body lost its immunity against antigen and prone to disease, which is accelerating premature aging.

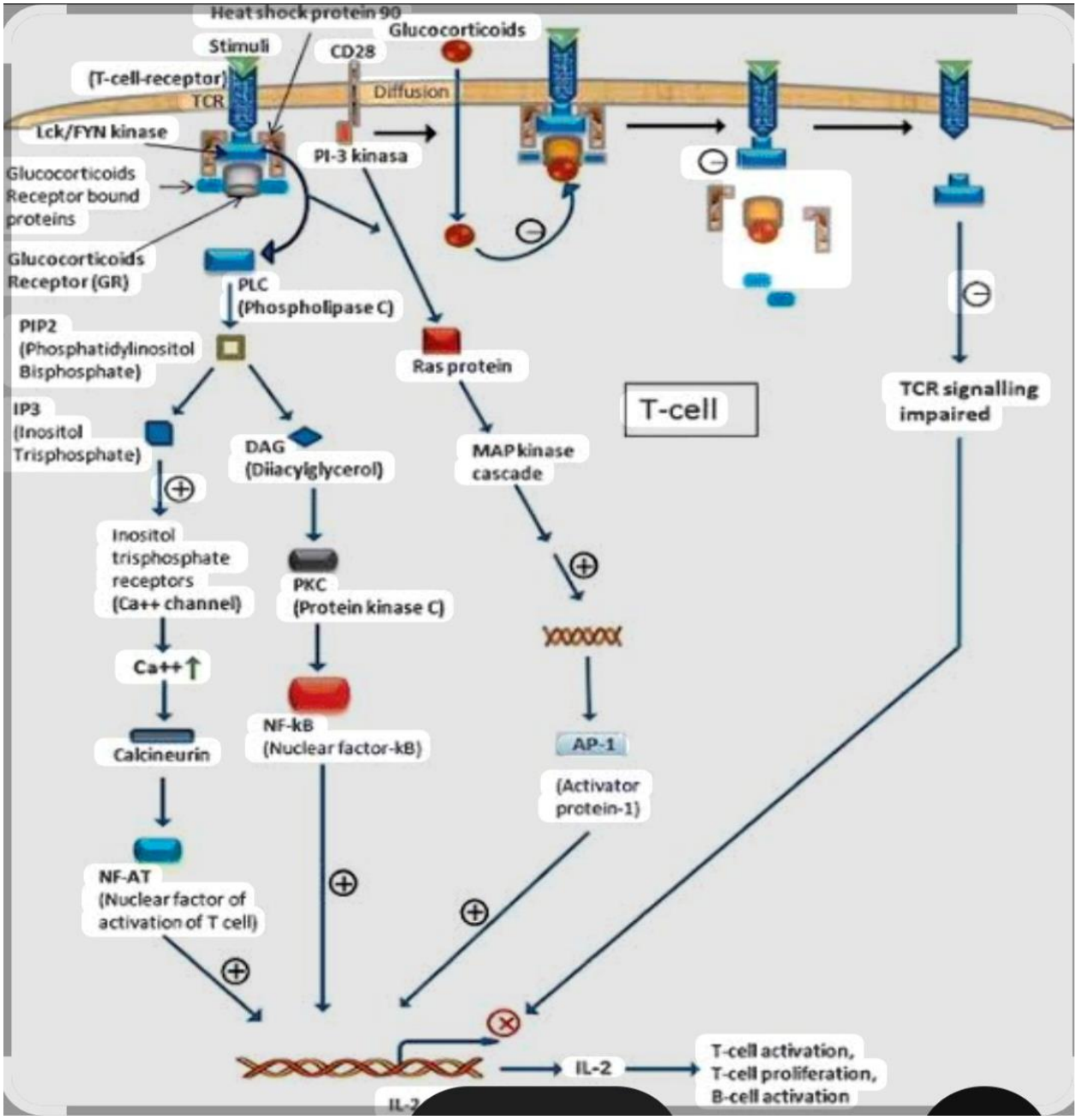


FIGURE 8.1: MECHANISM OF IMMUNOSUPPRESSION OF T-CELL ACTIVITY BY GCS IN CHRONIC STRESS

❖ GCs Inhibit Muscle Protein Synthesis And Cause Muscle Atrophy And Accelerated Aging:-

The age associated changes in body composition results from lower levels of anabolic hormones, neuromuscular alterations, decline in muscle protein synthesis, and a gradual /selective loss of muscle fibers.

Humorously, the reduction of myofibrillar protein synthesis in the elderly individual is not caused by a decline in the availability of mRNA encoding acting and myosin but alterations in post - translational events. However, GCs inhibit protein synthesis in skeletal muscle and stimulate muscle protein degradation which is responsible for muscle atrophy. The stimulatory effect of GCs on muscle proteolysis results from the activation of ubiquitin proteasome and lysosomal system. Increase in the components like ubiquitin, E2 enzyme(ubiquitin ligating enzyme), E3 enzyme and 26s proteasome of ubiquitin-proteasome pathway is synonymous with the activation of the pathway and this pathway is involved in the aging process of muscle.

The Akt/PKB (serine/threonine protein kinase) signaling pathway is one of the prerequisite for muscle protein synthesis which consists of growth factor receptor, adapter proteins like insulin receptor substrate (IRS), class I phosphor tidy inositol 3 kinase (PI3K) and Akt/PKB Kinases. Insulin like growth factor I receptor (IGF1R) signaling can prevent apoptosis and induce muscle protein synthesis which is mediated by PI3K.The binding of IGF 1 and IGF 2with IGF1R trigger the receptor's intrinsic tyrosine kinase activity. Consequently, IRSs phosphorylated and then interact with Src homology 2 domain of phosphatidylinositol 3 kinase (PI3K). Activated PI3K from lower levels of anabolic hormones, neuromuscular alterations, decline in muscle protein synthesis, and a gradual /selective loss of muscle fibers.

Humorously, the reduction of myofibrillar protein synthesis in the elderly individual is not caused by a decline in the availability of mRNA encoding acting and myosin but alterations in post-translational events. However, GCs inhibit protein synthesis in skeletal muscle and stimulate muscle protein degradation which is responsible for muscle atrophy.

The stimulatory effect of GCs on muscle proteolysis results from the activation of ubiquitin proteasome and lysosomal system. Increase in the components like ubiquitin, E2 enzyme from lower levels of anabolic hormones, neuromuscular alterations, decline in muscle protein synthesis, and a gradual / selective loss of muscle fibers.

Humorously, the reduction of myofibrillar protein synthesis in the elderly individual is not caused by a decline in the availability of mRNA encoding actin and myosin but alterations in post - translational events. However, GCs inhibit protein synthesis in skeletal muscle and stimulate muscle protein degradation which is responsible for muscle atrophy. The stimulatory effect of GCS on muscle proteolysis results from the activation of ubiquitin proteasome and lysosomal system Increase in the components like ubiquitin, E2 enzyme(ubiquitin ligating enzyme), E3 enzyme and 26s proteasome of ubiquitin-proteasome pathway is synonymous with the activation of the pathway and this pathway is involved in the aging process of muscle.

The Akt/PKB (serine/threonine protein kinase) signaling pathway is one of the prerequisite for muscle protein synthesis which consists of growth factor receptor, adapter proteins like insulin receptor substrate (IRS), class I phosphatidylinositol 3 kinase (PI3K) and Akt/PKB kinases. Insulin like growth factors 1 receptor (IGF1R) signaling can prevent apoptosis and induce muscle protein synthesis which is mediated by PI3K. The binding of IGF 1 and IGF 2 with IGF1R trigger the receptor's intrinsic tyrosine kinase activity. Consequently, IRSs phosphorylated and then interact with Src homology 2 domain of phosphatidylinositol 3 kinase (PI3K). Activated PI3K catalyzes the conversion of phosphatidylinositol - dependent-kinase 1 which phosphorylates The 308 residue on Akt which cause synthesis of muscle protein.

A further protective pathway activated by Akt involves inhibition of GSK3 (glycogen synthase kinase 3) which results from its phosphorylation at N terminal serine residue. Ultimately GSk3 catalyzes the phosphorylation and chronic stress induced glucocorticoid syntheses which activate glucocorticoid receptor (GRS), .Activated GRS negatively regulate PI3K and block the phosphorylation of PIP2.

Consequently, the normal pathway falls down and depletion of protein synthesis. Thus premature aging is accelerated protein degradation also occurs via UPS by GCs. Activated GRs positively regulates and increases the activity of Calpain, E2, E3 and 26s proteasome. As a result muscle protein is degraded and ultimately fallout in muscle atrophy leads to aging.

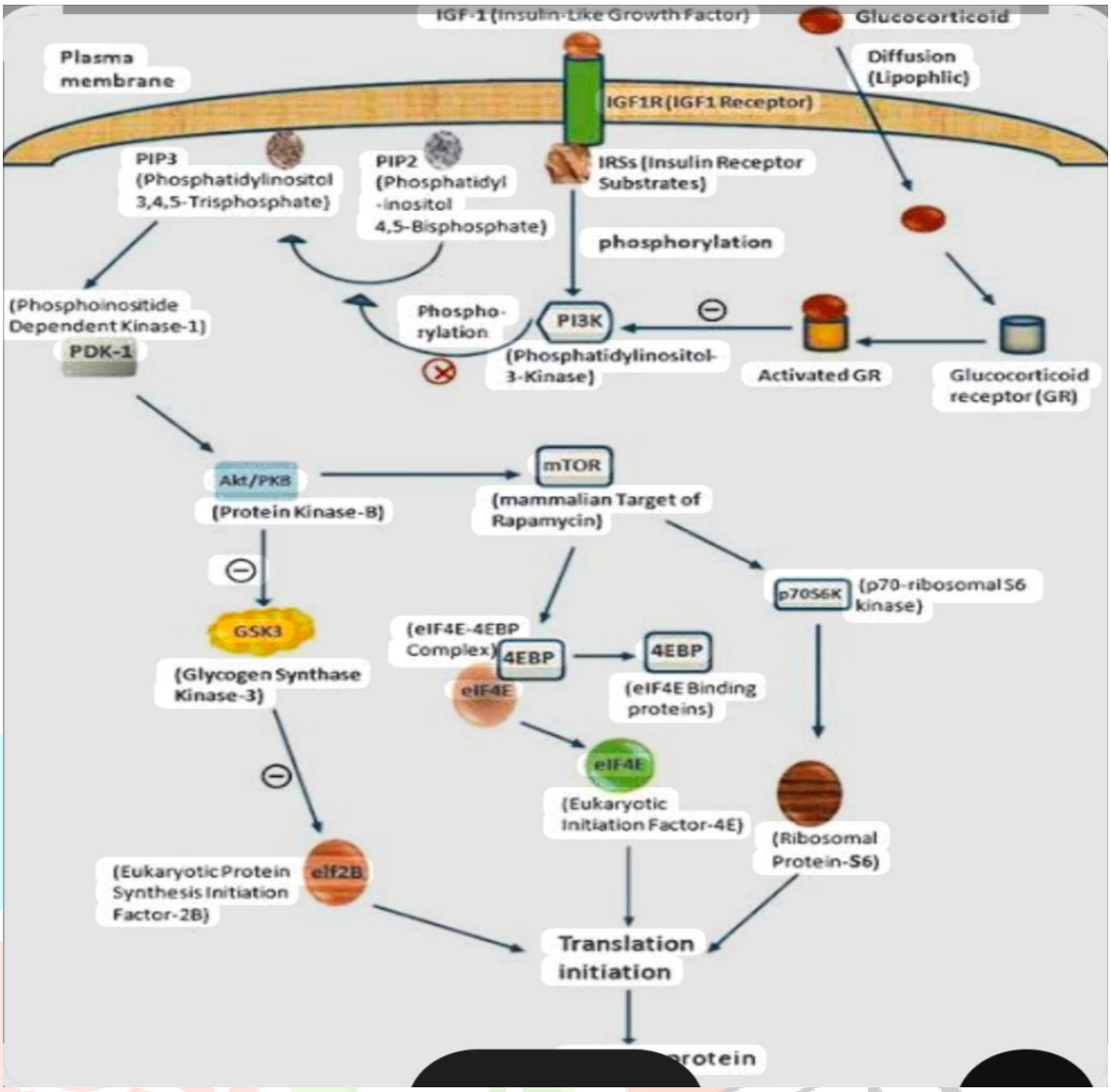


FIGURE 9: MECHANISM OF MUSCLE PROTEIN SYNTHESIS INHIBITED BY GCS

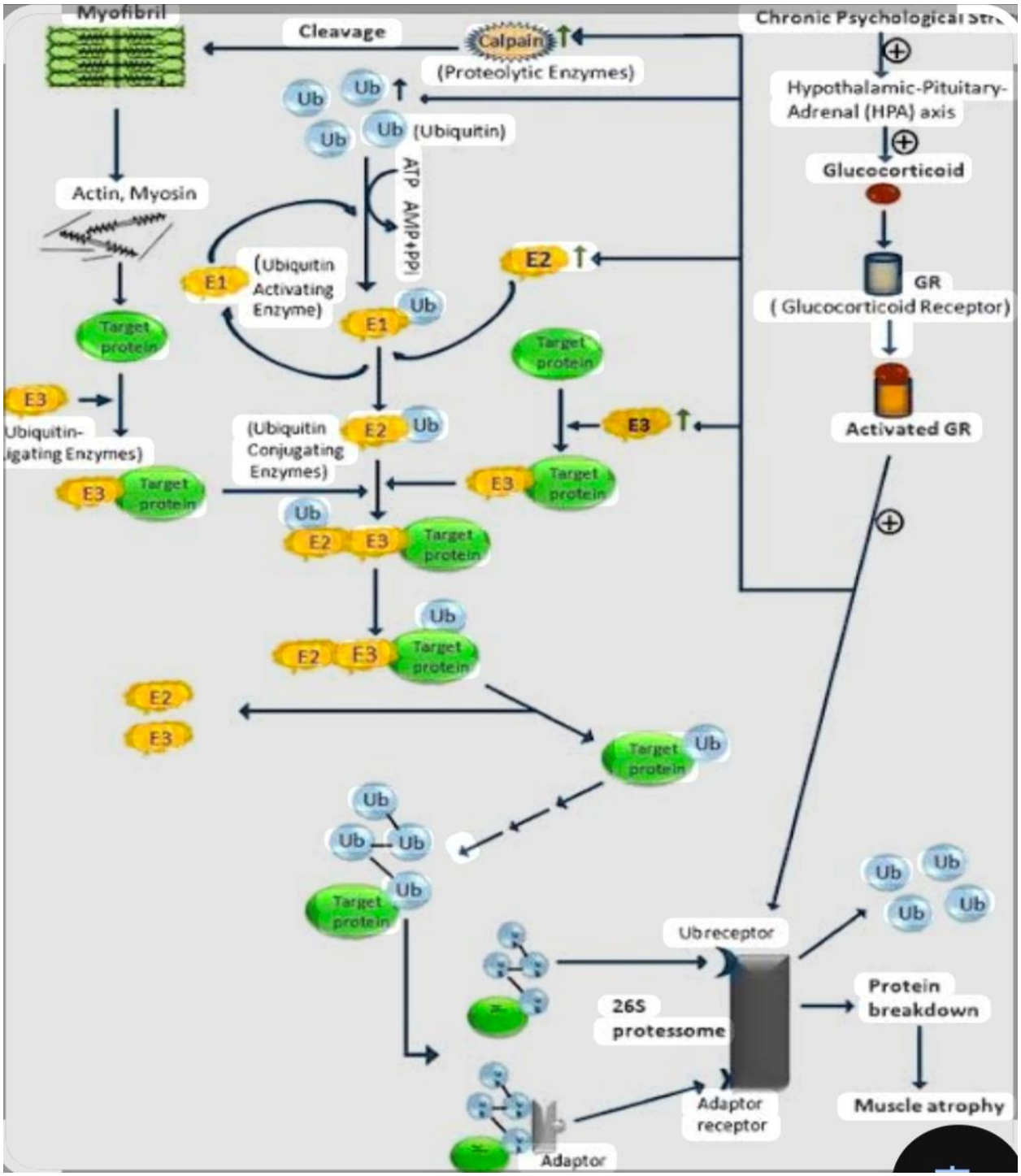


FIGURE 10: PROTEIN DEGRADATION VIA UPS BY GCS IN CHRONIC STRESS

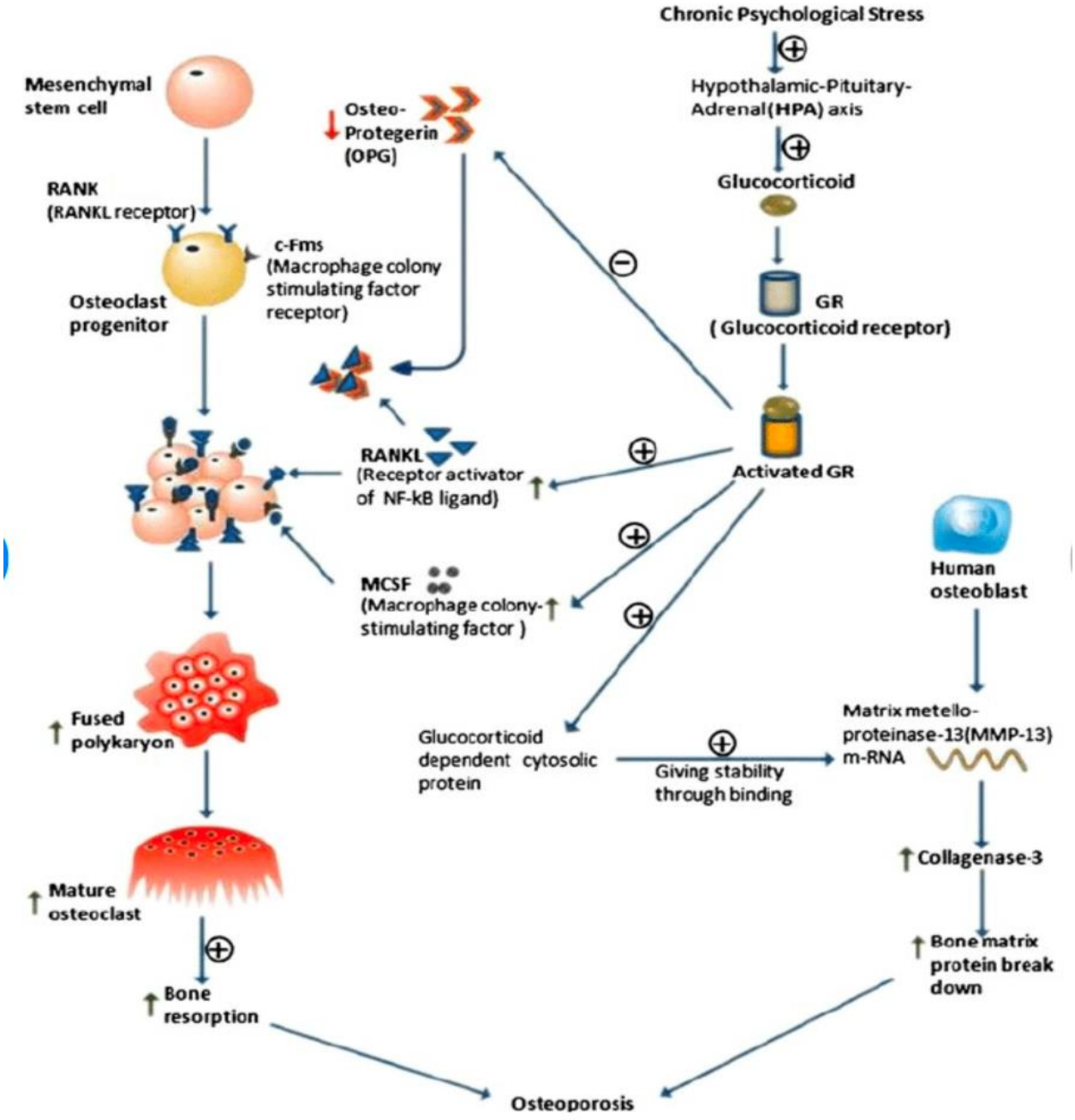


FIGURE 11: MECHANISM OF GCS INDUCED OSTEOPOROSIS

In stress GCs also amplify expression of collagenase 3 (MMP -13) that degrade type 1 collagen fibrils, the major component of the bone matrix. Furthermore, GCs enhance CSF-1 expression to induce osteoclast genesis in the presence of RANKL. GCs have a direct inhibitory effect on osteoblast mediated by three routes

1. Inhibition of the replication of osteoblastic lineage.
2. A decrease in the genesis of new osteoblastic cells.
3. Induction of osteoblastíc cell death in stress GCs also amplifies expression of collagenase 3 (MMP -13) that degrade type 1 collagen fibrils, the major component of the bone matrix. Furthermore, GCs enhance CSF-1 expression to induce osteoclast genesis in the presence of RANKL. GCs have a

direct inhibitory effect on osteoblast mediated by three routes **A)** Inhibition of the replication of osteoplastic lineage**. B)** A decrease in the genesis of new osteoblastic cells. **C)** Induction of osteoblastic cell death and apoptosis.

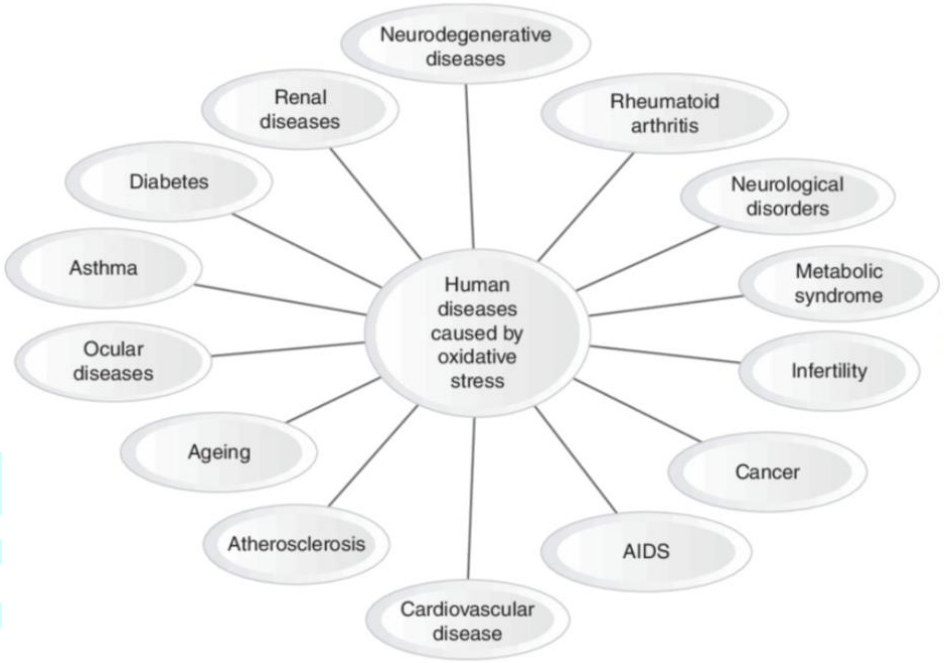


FIGURE 12: AN OVERVIEW OF CHRONIC STRESS LEADING TO ACCELERATE AGING

❖ CHRONIC STRESS, INSULIN RESISTANCE AND ADIPOSITY LEADING TO ACCELERATE AGING:-

Chronological age is strongly associated with increases in insulin resistance and adiposity, and it is becoming clear that long time exposure to insulin resistance accelerates biological aging. For example, in diabetes, there is early onset of certain diseases of aging, such as dementia, as well as signs of general body aging such as frailty. Chronic stress may accelerate these age related metabolic changes. Stress is related to obesity, especially abdominal obesity, and insulin resistance in both animal and human models. For example psychological stress, including job stress is associated with abdominal fat in cross-sectional and prospective studies.

These relationships are not surprising, as abdominal fat is an ideal target tissue for stress. Abdominal fat is regulated in part by A/C balance. Low levels of androgens and high levels of cortisol and insulin promote abdominal fat deposition. Visceral fat is well equipped to respond to the stress-induced combination of high cortisol and high insulin. For one, it has greater density of glucocorticoid receptors. Secondly, insulin promotes lipoprotein lipase, the fat storing enzyme that converts triglycerides

into stored fat (free fatty acids),and cortisol promotes prolonged elevations of lipoprotein lipase .Rodent studies have shown that the combination of stress plus high fat diet leads to greater abdominal fat storage than either stress or high fat diet alone.

In turn, abdominal fat contributes to numerous biochemical stressors. Clinically greater abdominal fat thickness is associated with high levels of systemic total oxidative stress (lower antioxidant, higher lipid markers) and greater number of inflammatory markers. Fat cells, subcutaneous, abdominal, and particularly visceral abdominal fat, release cytokines such as TNF a and IL-6. Monocyte infiltrate the fat, especially near dead cells, and further release cytokines, promoting systemic inflammation Animals with fat transplant of visceral but not subcutaneous origin develop increased inflammatory and cardiovascular diseases, suggesting that inflammation alone is pathogenic. Thus, the visceral fat tissue is a likely source of the chemicals that induce cellular aging.

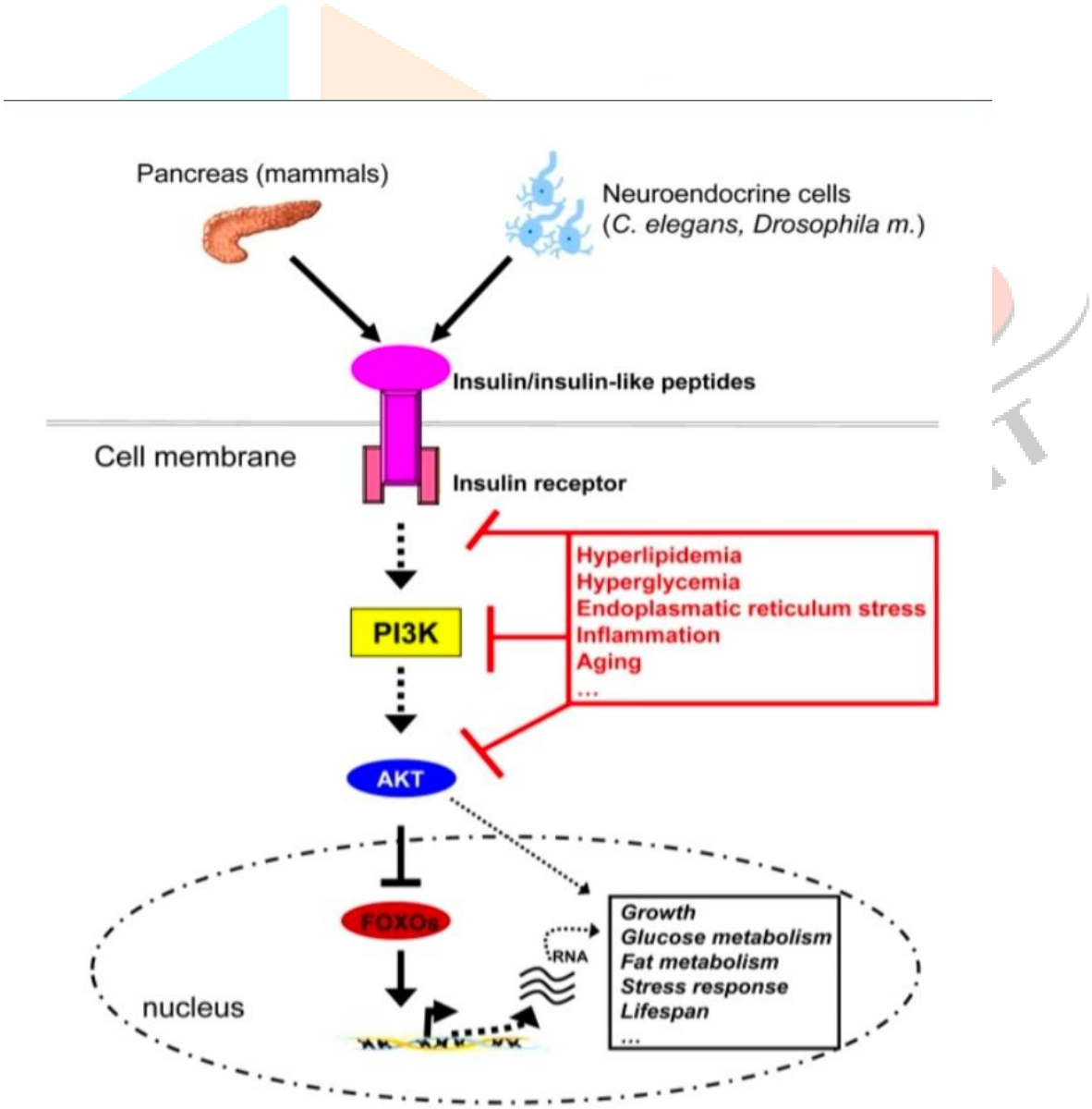


FIGURE 13: SHOWING HOW AGING IS ACCELERATED BY INSULIN IN STRESS CONDITION

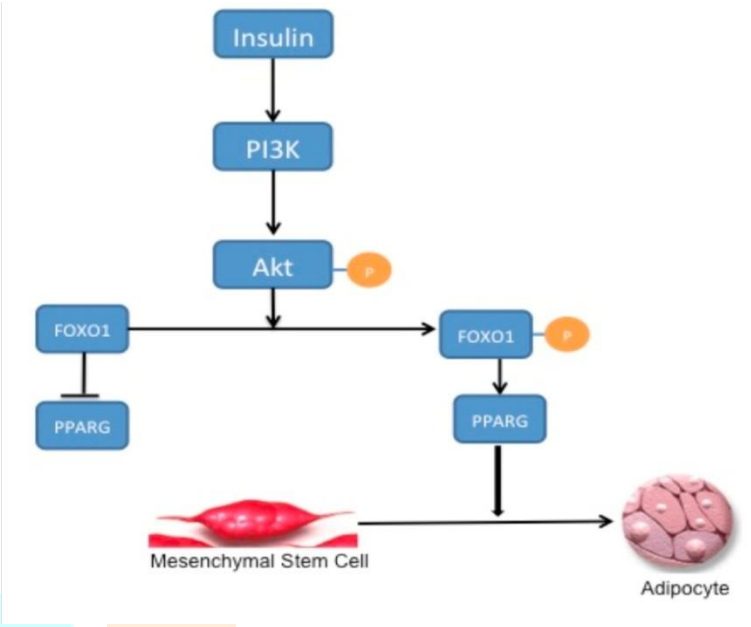


FIGURE 14: HOW INSULIN HELPS IN ADIPOGENESIS

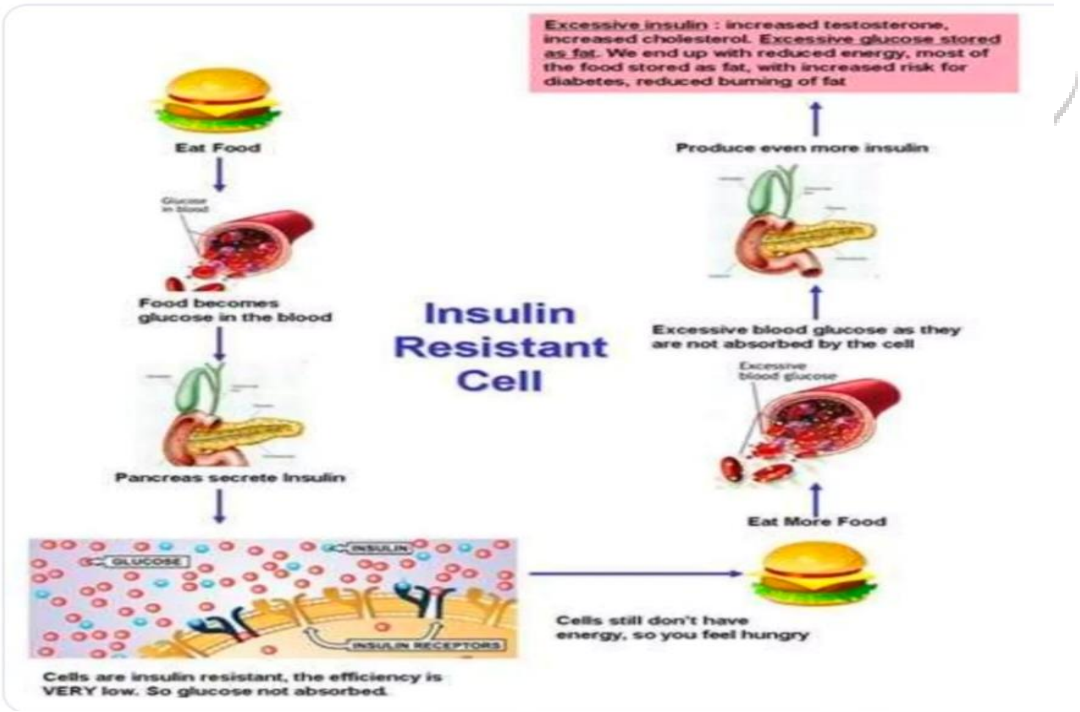


FIGURE 15: HOW INSULIN RESISTANCE CAUSE ABDOMINAL FAT STORAGE

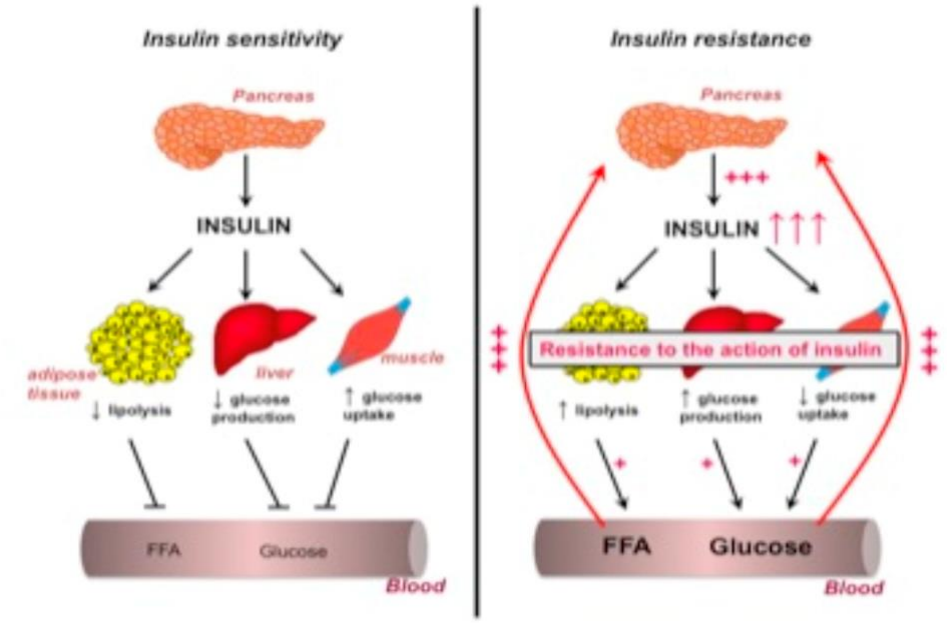


FIGURE 16: SHOWING INSULIN SENSITIVITY & INSULIN RESISTANCE

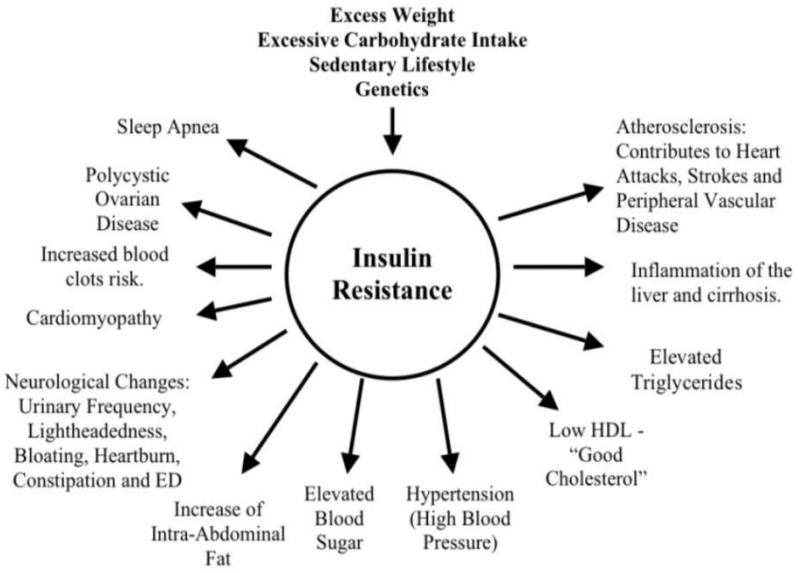


FIGURE 17: SHOWING HOW INSULIN CAUSE AGING

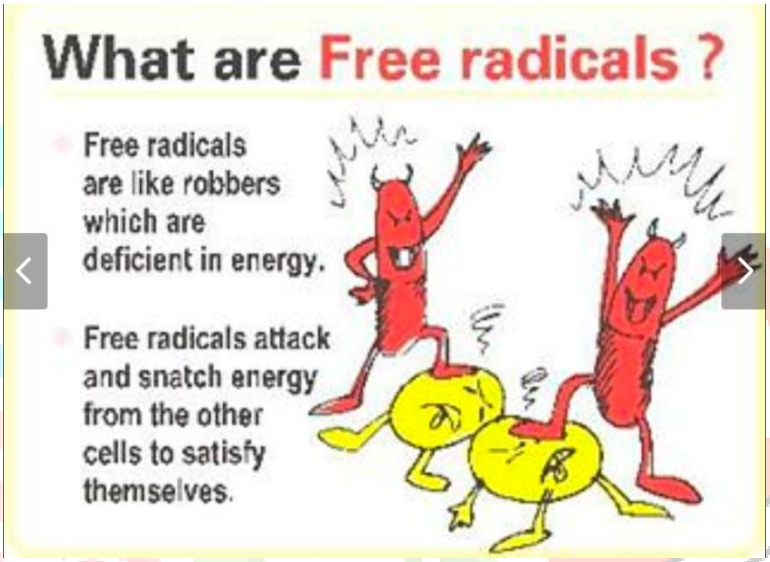
❖ OXIDATIVE STRESS ACCELERATE AGING:-

Production of free radicals (oxidative stress) is thought to exert a major influence on cell aging and tissue damage, particularly to cardiac cells and the brain. Free radicals tend to increase with age, as indexed by markers such as lipid peroxidation and impaired antioxidant activity. However, in elderly individuals who are still healthy, oxidative stress level can be similar to that of in young adults, or at least

comparable to antioxidant defenses, suggesting that oxidation is not inevitable in aging. It appears that psychological stress and lifestyle factors such as smoking sedentariness have an impact on the level of oxidation. Oxidation in turn associated with functional decline and might be partly responsible for whole body accelerated aging. In an elderly population(>80 years old), free radicals were associated with proper cognitive function loss of autonomy, loss of ability to perform daily activities , and institutionalization, as well as depressive symptom.

Oxidative stress appears to play an especially important role in brain. A/C imbalance may affect free radical production and neurodegenerative diseases. Cortisol is essential for brain viability. However, when it is too high for too long, certain vulnerable neurons may be damaged.

In part by increases in oxidative stress .DHEA and estrogens can prevent oxidative stress damage in neurons. DHEA can block cortisol- mediated excitatory neurotoxicity, pointing to the likely importance of the balance between cortisol and DHEA.



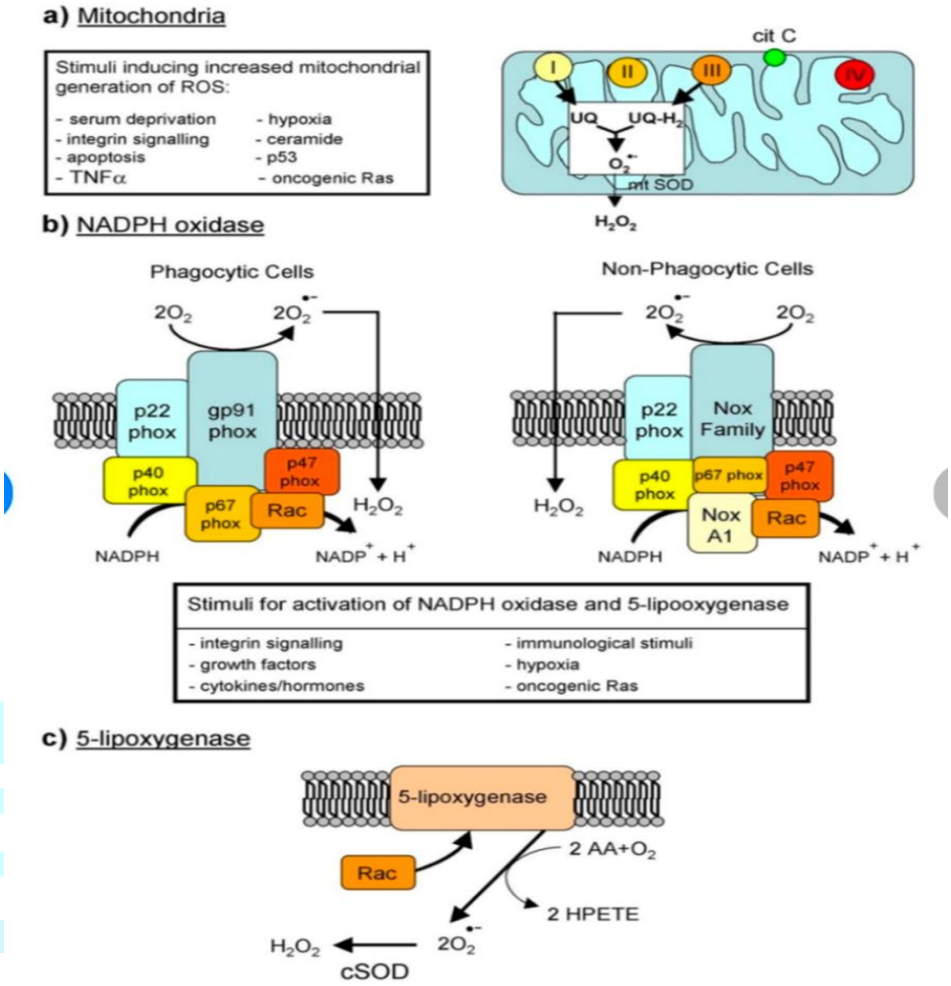


FIGURE 18: SOURCES FROM WHICH ROS (REACTIVE OXYGEN SPECIES) IS PRODUCED

There are a growing number of studies both in rats and humans that have found links between markers of oxidative stress and physiological distress. Markers of oxidative stress are increased by acute stress exposure as well as by chronic states, such as major depression and duration of exposure to caregiving. In one study of acute stress individual who responded with higher ratings of anger and tendency to suppress anger had greater reactive oxygen species 30 minutes after the acute stressor.

However, other studies found that acute stress may reduce markers of oxidation. It may be that both the stat of a person's health and antioxidant defenses together determines whether acute stress leads to increases or decreases in net oxidation.

The links between psychological stress and blood levels of oxidative stress may be mediated in part by increases in cortisol and insulin, although there is no direct evidence of this at present. Elevation of glucose and insulin, from chronic stress may promote free radical production through auto-oxidative glycosylation and through insulin mediated sympatheticactivity.

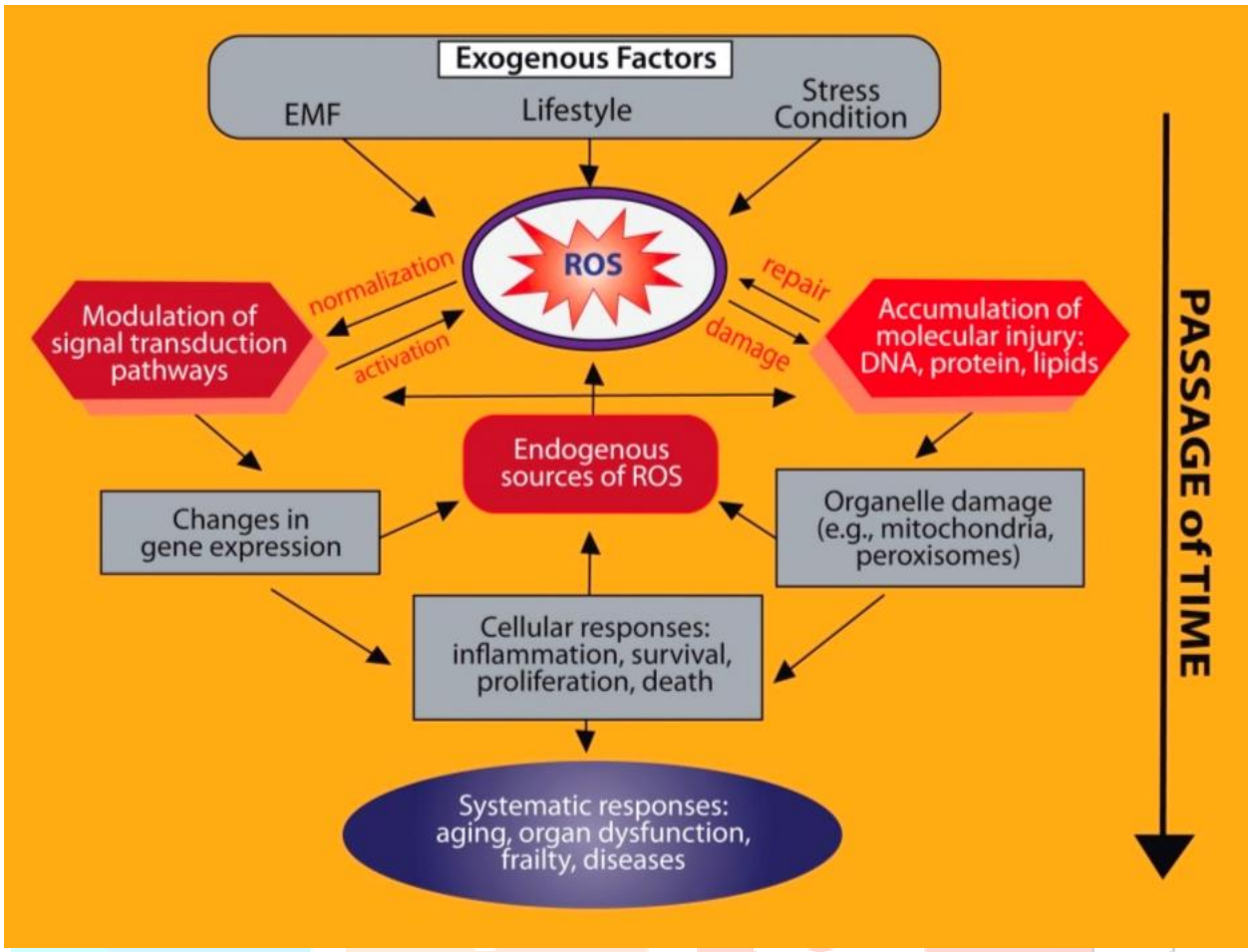


FIGURE 19: ROS CAUSES CELLULAR DAMAGES LEADS TO ACCELERATE AGING

- **ROS Also Cause DNA Damage And Accelerate Aging**:-

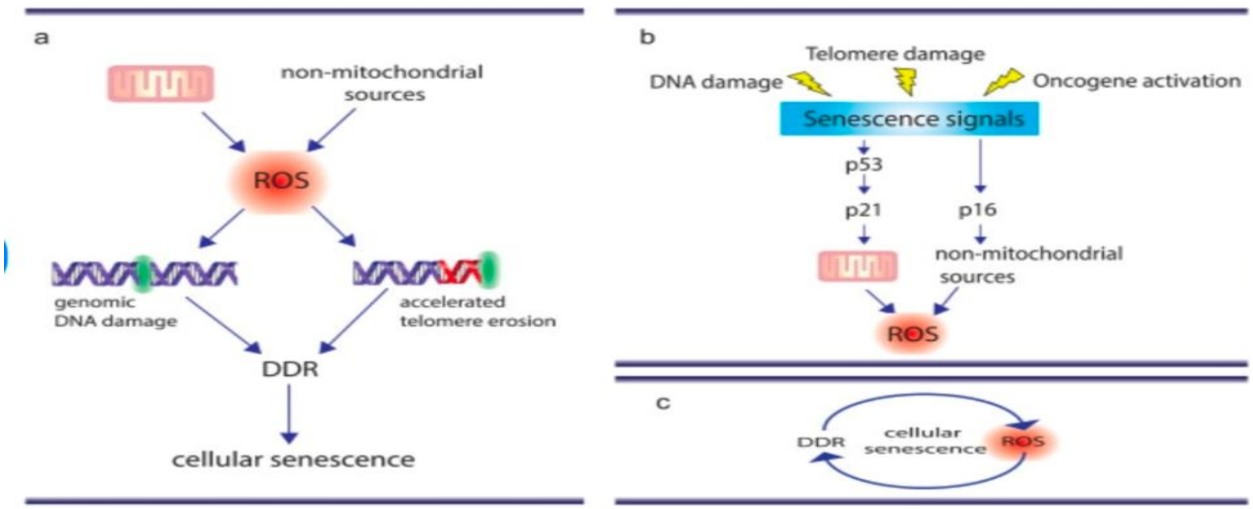


FIGURE 20: TWO DIFFERENT MODELS BY WHICH REACTIVE OXYGEN SPECIES CAN IMPACT ON AGING

In figure 20 - a) reactive oxygen species (ROS) produced via mitochondrial and non-mitochondrial sources induce genomic DNA damage and accelerate telomere erosion/damage, both of which contribute to activation of a DNA damage response(DDR).

b) ROS can act as signaling molecules in aging: activation of 'senescence signals' has been shown to result in increased ROS generation (mitochondrial and non-mitochondrial). ROS has been shown to impact on a variety of pathways which may help stabilize the senescence growth arrest.

c) Simplified feedback loop model involving ROS and DNA damage. Telomere uncapping or general DNA damage triggers a DDR which culminates through yet unidentified process to ROS generation. ROS generation leads to additional DNA damage to the genome, stabilizing the DDR and leading to a stable senescence arrest.

❖ CHRONIC STRESS, MELATONIN AND SKIN AGING:-

Chronic stress decreases the melatonin hormone from the pineal synthesized at night, which serve as anti-aging factor in human. Like the whole organism, skin follows the process of aging during life-time. Additional to internal factors, several environmental factors, such as solar radiation, considerably contribute to this process. While fundamental mechanisms regarding skin aging are known, new aspects of anti-Aging agents such as melatonin are introduced. Melatonin is a hormone produced in the glandula pinealis that follows a circadian light-dependent rhythm of secretion. It has been experimentally implicated in skin functions such as hair cycling and fur pigmentation and melatonin receptors are expressed in many skin cell types including normal and malignant keratinocytes, melanocytes and fibroblasts. It possesses a wide range of endocrine properties as well as strong ant oxidative activity. Regarding UV-induced solar damage, melatonin distinctly counteracts massive generation of reactive oxygen species, mitochondrial and DNA damage. Thus, there is considerable evidence for melatonin to be an effective anti-skin aging compound.

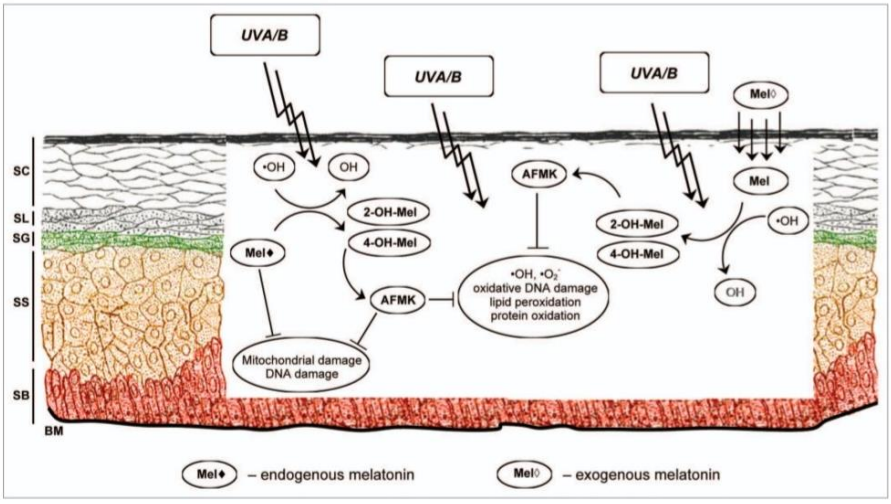


FIGURE 21: THE MELATONERGIC ANTI OXIDATIVE SYSTEM IN HUMAN SKIN

Melatonin regulates the synthesis of other hormones, as it lipophilic and pass through all morphological, blood-brain and placental barrier so it acts as scavenger of free radicals. As chronic stress cause in somnia it

decreases melatonin synthesis because melatonin is synthesized in dark phase and increases with duration of sleeping.

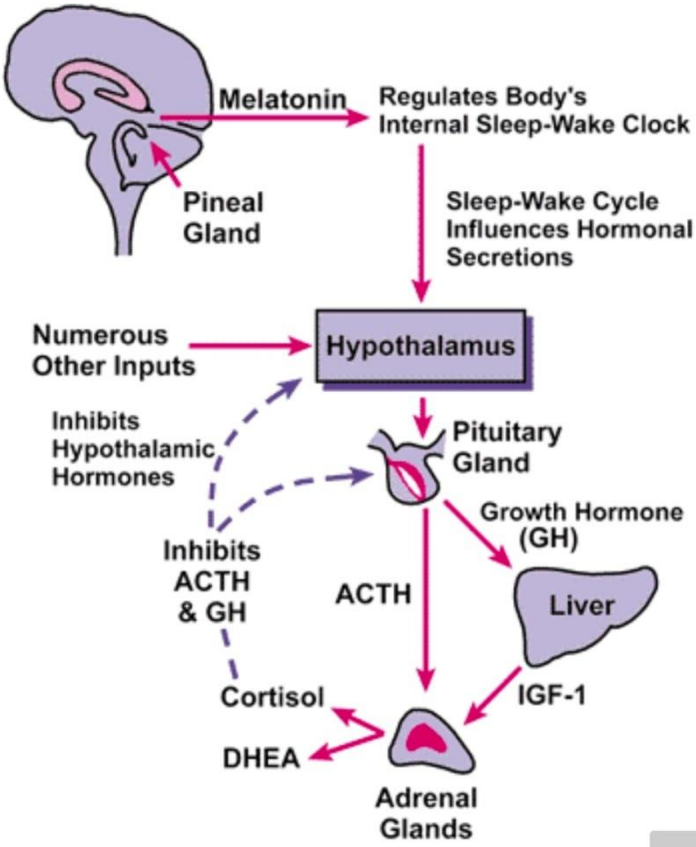


FIGURE 22: HOW MELATONIN REGULATE SYNTHESIS OF OTHER HORMONES

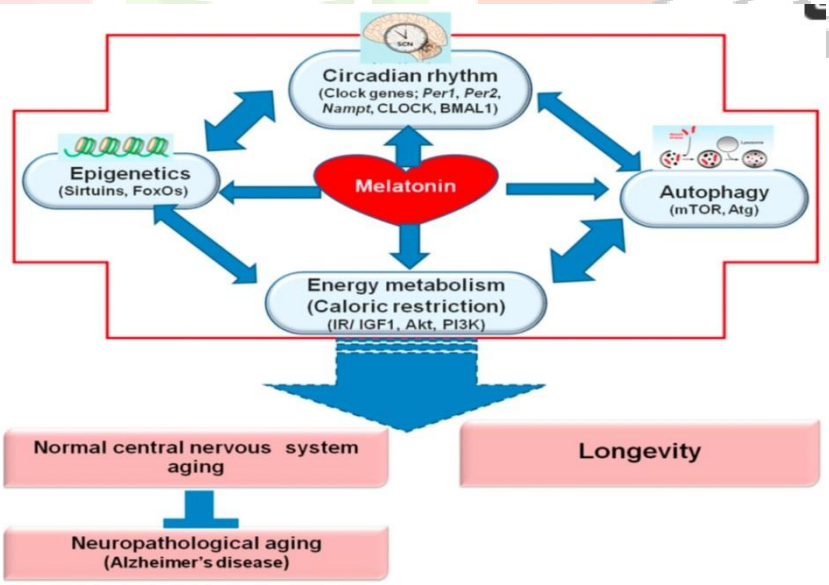


FIGURE 23: MELATONIN ACTS AS ANTI-AGING FACTOR

❖ HEALTH BEHAVIOUR AND CHRONIC STRESS:-

Health behaviors are important contributors to A/C imbalance and other biochemical stressors. Health behaviors including activity, diet, and sleep shape our hormonal milieu. Sedentariness, a

high fat diet, and insufficient sleep have been associated with higher HPA axis and/or lower GH axis responsiveness and higher insulin levels. Lifestyle factors have also been linked to DNA damage due to oxidation. For example, smoking, alcohol, and a high fat diet are associated with greater oxidative stress.

- **CHRONIC HPA ACTIVATION, CHRONIC ALCOHOL EXPOSURE, SMOKING AND PREMATURE AND EXAGGERATED AGING**:-

To date, researchers have not investigated alcohol's acute and chronic effects on HPA activity in elderly humans. However, many of the symptoms associate with excessive cortisol production in patients with Cushing's syndrome (e.g. diabetes, muscle weakness, osteoporosis, atherosclerosis, hypertension, memory impairment, wasting away of brain tissue, sleep disturbances, and compromised immunity) also commonly occur in elderly people, especially those who abuse alcohol, This overlap of the symptoms of aging and of among chronic cortisol overexposure suggests that alcohol-induced excessive cortisol secretion is, at least in part, responsible for the premature or exaggerated aging seen in many alcoholics.

As described earlier, the chronic elevation of glucocorticoid levels may contribute to nerve cell degeneration in the hippocampus. Neuroimaging studies of the brains of living alcoholics, however, found significant reductions in the sizes of other brain areas in addition to the anterior hippocampus. Although the hippocampus is structurally related to the cortex, glucocorticoids do not appear to have a degenerative effect on the cortex in general. Researchers must therefore determine whether elevated cortisol levels contribute to a general alcohol-induced neuro-degeneration or account only for hippocampal degeneration. Even a selective cortisol-mediated alcohol effect on the hippocampus is of serious concern because of the central role of that brain region in memory process.

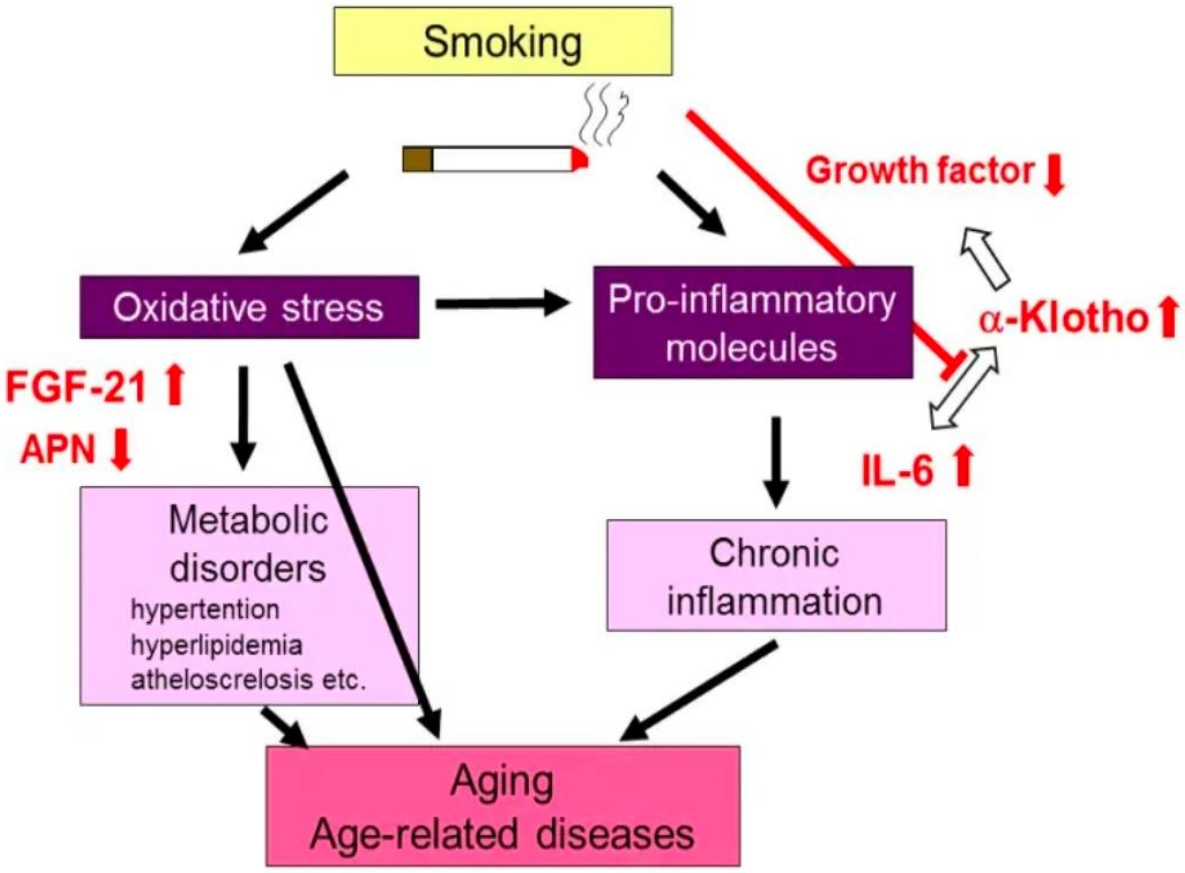


FIGURE 24: SMOKING ACCELERATE AGING

❖ **CHRONIC STRESS, COFFEE & AGING:-**

We depend on coffee to decrease our stress but research stress chronic coffee consumption with chronic stress accelerate aging. Coffee has several harmful affect that leads to premature aging.

- Coffee lowers the production of DHEA which acts as anti-glucocorticoid.
- Coffee increase blood vessel stiffness.
- Coffee increases heart attack risk.
- Coffee increases serum cholesterol level.
- Coffee causes heart rhythm irregularity.
- Chronic metabolic acidity associated with coffee consumption stimulates cortisol secretion, further activating stress response leading to a more rapid aging process.
- Coffee also raises blood pressure.

Thus coffee consumption with chronic stress accelerates cellular aging,

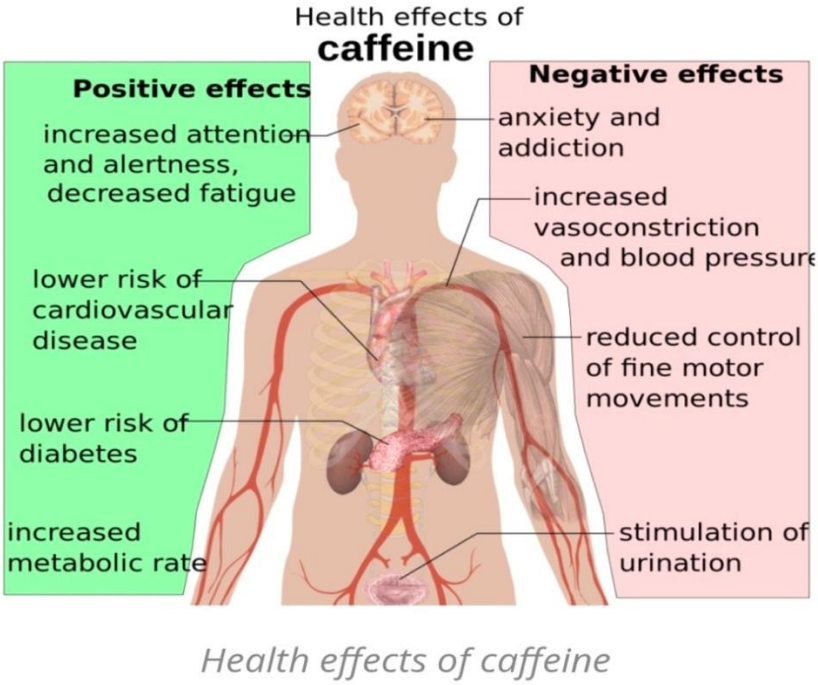


FIGURE 25: HARMFUL EFFECTS OF COFFEE OR CAFFEINE

❖ CONCLUSION:-

The large suite of catecholamine and GC response is believed to be the essential in surviving stressors. Clearly the lack of epinephrine and norepinephrine release, i.e. the fight or flight response, would be devastating during a predatory attack. Similarly, animals that lack GCs are unable to mount an effective response to stressors in order to promote survival.

On the other hand, long term of chronic release of these hormones can be detrimental. Repeated or constant activation of the fight or flight response leads to cardiovascular disease. Similarly the individuals exposed to long term or chronic GCs suffer from a number of diseases including diabetes, depression, reproductive dysfunction, and immune suppression. Consequently, responses to acute stressors generally enhance fitness, but long term exposure can decrease fitness. Clearly, successful long term survival requires balancing acute release while minimizing chronic exposure.

❖ REFERENCE:-

1. Wan H, Sengupta M, Velkoff VA, DeBarros KA, 2005 65+ in the United States. US Census Bureau [http://www.census.gov/prod/2006pubs/p23-209.pdf. Accessed.
2. Bosma H, Stansfeld SA, Marmot MG, Peter R, Siegrist J, Marmot M, 1998 Job control, personal characteristics, and heart disease: Two alternative job stress models and the risk of coronary heart disease. J Occup Health Psychol 3: 402–409. DOI: 10.1037/1076-8998.3.4.402
3. Chrousos G, Gold P, 1992 The concepts of stress and stress system disorders. JAMA 267: 1244–1252. DOI: 10.1001/jama.1992.03480090092034
4. McEwen B, 1998 Protective and damaging effects of stress mediators. New England Journal of Medicine 338: 171–179. DOI: 10.1056/NEJM199801153380307
5. Musselman D, Evans D, Nemeroff C, 1998 The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry 55: 580–592. DOI: 10.1001/archpsyc.55.7.580
6. Stansfeld SA, Fuhrer R, Shipley MJ, Marmot MG, 2002 Psychological distress as a risk factor for coronary heart disease in the Whitehall II Study. Int J Epidemiol 31: 248–255. DOI: 10.1093/ije/31.1.248
7. Sterling P, Eyer J, 1988 Allostasis: A new paradigm to explain arousal pathology. In: Fisher S, Reason J, eds. Handbook of Life Stress: Cognition and Health: John Wiley & Sons, Ltd; pp, 629–649.
8. Bower J, Low C, Moskowitz J, Sepah S, Epel E, 2008 Pathways from benefit finding to physical health: Enhanced psychological and physiological responses to stress. Social and Personality Psychology Compass; in press.
9. Seeman T, Robbins R, 1994 Aging and hypothalamic-pituitary-adrenal response to challenge in humans. Endocr Rev 15: 233–259.
10. Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC, 2005 A meta-analysis of cortisol response to challenge in human aging: importance of gender. Psychoneuroendocrinology 30: 80–91. DOI: 10.1016/j.psyneuen.2004.06.002
11. Seeman T, Singer B, Rowe J, McEwen B, 2001 Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci USA 98: 4770–4775. DOI: 10.1073/pnas.081072698
12. Epel E, Burke H, Wolkowitz O 2007 Psychoneuroendocrinology of Aging: Focus on anabolic and catabolic hormones. In: Aldwin C, Spiro A, Park C, eds. Handbook of Health Psychology of Aging: Guildford Press; pp, 119–141.
13. Dallman MF, la Fleur SE, Pecoraro NC, Gomez F, Houshyar H, Akana SF, 2004 Mini review: glucocorticoids—food intake, abdominal obesity, and wealthy nations in 2004. Endocrinology 145: 2633–2638. DOI: 10.1210/en.2004-0037
14. Strack A, Sebastian R, Schwartz M, Dallman M, 1995 Glucocorticoids and insulin: reciprocal signals for energy balance. Am J Physiol 268: R142–R149.
15. Melamed S, Ugarten U, Shirom A, Kahana L, Lerman Y, Froom P, 1999 Chronic burnout, somatic arousal, and elevated salivary cortisol levels. J Psychosom Res 46: 591–598. DOI: 10.1016/S0022-3999(99)00007-0
16. Steptoe A, Cropley M, Griffith J, Kirschbaum C, 2000 Job strain and anger expression predict early morning elevations in salivary cortisol. Psychosom Med 62: 286–292. DOI: 10.1097/00006842-200003000-00022
17. Vedhara K, Cox N, Wilcock G, et al, 1999 Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. The Lancet 353: 627–631. DOI: 10.1016/S0140-6736(98)06098-X

18. Burton F, Hinton J, Neilson E, Beastall G, 1996 Concentrations of sodium, potassium and cortisol in saliva, and self-reported chronic work stress factors. Biol Psycho 142: 425–438. DOI: 10.1016/0301-0511(95)05171-6
19. Irwin M, Hauger R, Patterson T, Semple S, Ziegler M, Grant I, 1997 Alzheimer caregiver stress: basal natural killer cell activity, pituitary adrenal cortical function, and sympathetic tone. Ann Behav Med 1997: 83–90. DOI: 10.1007/BF02883324
20. Pike J, Smith T, Hauger R, et al, 1997 Chronic life stress alters sympathetic, neuroendocrine, and immune responsivity to an acute psychological stressor in humans. Psychosom Med 59: 447–457. DOI: 10.1097/00006842-199707000-00015
21. Gold PW, Chrousos GP, 2002 Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Mol Psychiatry 7: 254–275. DOI: 10.1038/sj.mp.4001032
22. Fries E, Hesse J, Hellhammer J, Hellhammer DH, 2005 A new view on hypocortisolism. Psychoneuroendocrinology 30: 1010–1016. DOI: 10.1016/j.psyneuen.2005.04.006
23. Bower J, Ganz P, Aziz N, 2007 Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. Psychosom Med 67: 277–280. DOI: 10.1097/01.psy.0000155666.55034.c6
24. Raison CL, Miller AH, 2003 When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. Am J Psychiatry 160: 1554–1565. DOI: 10.1176/appi.ajp.160.9.1554
25. Ding EL, Song Y, Malik VS, Liu S, 2006 Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 295: 1288–1299. DOI: 10.1001/jama.295.11.1288
26. Barrett-Connor E, Ferrara A, 1996 DHEA, DHEAS, obesity, WHR, and NIDDM in postmenopausal women: The Rancho Bernardo Study. J Clin Endocrinol Metab 81: 5–64.
27. Dandona P, Dhindsa S, Chaudhuri A, Bhatia V, Topiwala S, Mohanty P, 2008 Hypogonadotrophic hypogonadism in type 2 diabetes, obesity and the metabolic syndrome. Curr Mol Med 8: 816–828. DOI: 10.2174/156652408786733658
28. Morrison M, 1996 Hormones, Gender and the Aging Brain: The Endocrine Basis of Geriatric Psychiatry: Cambridge University Press.
29. Heuser I, Deuschle M, Luppa P, Schweiger U, Standhardt H, Weber B, 1998 Increased diurnal plasma concentrations of dehydroepiandrosterone in depressed patients. J Clin Endocrinol Metab 83: 3130–3133. DOI: 10.1210/jcem.83.9.5081
30. Kyrou I, Tsigos C, 2008 Chronic stress, visceral obesity and gonadal dysfunction. Hormones (Athens) 7: 287–293. DOI: 10.14310/horm.2002.1209
31. Maninger N, Wolkowitz OM, Epel ES, Reus V, Mellon S, 2008 Neurobiological and Neuropsychiatric Effects of Dehydroepiandrosterone (DHEA) and DHEA Sulfate (DHEAS). Front Neuroendocrinol 30: 65–91. DOI: 10.1016/j.yfrne.2008.11.002
32. Anker SD, Chua TP, Ponikowski P, et al, 1997 Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation 96: 526–534. DOI: 10.1161/01.CIR.96.2.526
33. Jankowska EA, Biel B, Majda J, et al, 2006 Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. Circulation 114: 1829–1837. DOI: 10.1161/CIRCULATIONAHA.106.649426
34. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR, 2006 Low serum testosterone and mortality in male veterans. Arch Intern Med 166: 1660–1665. DOI: 10.1001/archinte.166.15.1660

35. Maggio M, Lauretani F, Ceda GP, et al, 2007 Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the Chianti Area (InCHIANTI) study. Arch Intern Med 167: 2249–2254. DOI: 10.1001/archinte.167.20.2249
36. Hankinson SE, Willett WC, Colditz GA, et al, 1998 Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 351: 1393–1396. DOI: 10.1016/S0140-6736(97)10384-1
37. Laron Z, 2008 The GH-IGF1 axis and longevity. The paradigm of IGF1 deficiency. Hormones (Athens) 7: 24–27. DOI: 10.14310/horm.2002.1111034
38. Berryman DE, Christiansen JS, Johannsson G, Thorner MO, Kopchick JJ, 2008 Role of the GH/IGF-1 axis in lifespan and healthspan: Lessons from animal models. Growth Horm IGF Res 18: 455–471. DOI: 10.1016/j.ghir.2008.05.005
39. Willcox BJ, Donlon TA, He Q, et al,, 2008, FOXO3A genotype is strongly associated with human longevity. Proc Natl Acad Sci USA 105: 13987–13992. DOI: 10.1073/pnas.0801030105
40. Morley J, 2008 Diabetes and aging: epidemiologic overview. Clin Geriatr Med 24: 395–405. DOI: 10.1016/j.cger.2008.03.005
41. Bjorntorp P, Rosmond R, 1999 Hypothalamic origin of the metabolic syndrome. The Metabolic Syndrome. Vol 892. New York, NY: Annals of the New York Academy of Sciences. DOI: 10.1111/j.1749-6632.1999.tb07803.x
42. Brindley D, Rolland Y, 1989 Possible connections between stress, diabetes, obesity, hypertension and altered lipoprotein metabolism that may result in atherosclerosis. Clin Sci 77: 453–461. DOI: 10.1042/cs0770453
43. Dallman MF, Pecoraro NC, la Fleur SE, 2005 Chronic stress and comfort foods: self-medication and abdominal obesity. Brain Behav Immun 19: 275–280. DOI: 10.1016/j.bbi.2004.11.004
44. Epel E, McEwen B, Seeman T, et al, 2000 Stress and body shape: Consistently greater stress-induced cortisol reactivity among women with abdominal fat. Psychosom Med 62: 623–632. DOI: 10.1097/00006842-200009000-00005
45. Rosmond R, Lapidus L, Marin P, Bjorntorp P, 1996 Mental distress, obesity, and body fat distribution in middle-aged men. Obes Res 4: 245–252. DOI: 10.1002/j.1550-8528.1996.tb00542.x
46. Kouvonen A, Kivimaki M, Cox SJ, Cox T, Vahtera J, 2005 Relationship between work stress and body mass index among 45, 810 female and male employees. Psychosom Med 67: 577–583. DOI: 10.1097/01.psy.0000170330.08704.62
47. Kivimaki M, Head J, Ferrie JE, et al, 2006 Work stress, weight gain and weight loss: evidence for bidirectional effects of job strain on body mass index in the Whitehall II study. Int J Obes (Lond) 30: 982–987. DOI: 10.1038/sj.ijo.0803229
48. Korkeila M, Kaprio J, Rissanen A, Koshenvuo M, Sorensen TI, 1998 Predictors of major weight gain in adult Finns: stress, life satisfaction and personality traits. Int J Obes Relat Metab Disord 22: 949–957. DOI: 10.1038/sj.ijo.0800694
49. Brunner EJ, Chandola T, Marmot MG, 2007 Prospective effect of job strain on general and central obesity in the Whitehall II Study. Am J Epidemiol 165: 828–837. DOI: 10.1093/aje/kwk058
50. Bjorntorp P, 1996 The regulation of adipose tissue distribution. Int J Obes Relat Metab Disord 20: 291–302.
51. Dallman M, Pecoraro N, Akana S, et al, 2003 Chronic stress and obesity: A new view of "comfort food." PNAS; 100: 11696–11701. DOI: 10.1073/pnas.1934666100

52. Rebuffe-Scrive M, Walsh U, McEwen B, Rodin J, 1992 Effect of chronic stress and exogenous glucocorticoids on regional fat distribution and metabolism. Physiol Behav 52: 583–590. DOI: 10.1016/0031-9384(92)90351-2
53. Appel B, Fried SK, 1992 Effects of insulin and dexamethasone on lipoprotein lipase in human adipose tissue. Am J Physiol 262: E695–699.
54. Kuo LE, Kitlinska JB, Tilan JU, et al, 2007 Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome. Nat Med 13: 803–811. DOI: 10.1038/nm1611
55. Ohman MK, Shen Y, Obimba CI, et al, 2008 Visceral adipose tissue inflammation accelerates atherosclerosis in apolipoprotein E-deficient mice. Circulation 117: 798–805. DOI: 10.1161/CIRCULATIONAHA.107.717595
56. Palmieri VO, Grattagliano I, Portincasa P, Palasciano G, 2006 Systemic oxidative alterations are associated with visceral adiposity and liver steatosis in patients with metabolic syndrome. J Nutr 136: 3022–3026. DOI: 10.1093/jn/136.12.3022
57. Pou KM, Massaro JM, Hoffmann U, et al, 2007 Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation 116: 1234–1241. DOI: 10.1161/CIRCULATIONAHA.107.710509
58. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S, 2007 Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes 56: 1010–1013. DOI: 10.2337/db06-1656
59. Beckman KB, Ames BN, 1998 The free radical theory of aging matures. Physiol Rev.; 78: 547–581. DOI: 10.1152/physrev.1998.78.2.547
60. Finkel T, Holbrook NJ, 2000 Oxidants, oxidative stress and the biology of ageing. Nature 408: 239–247. DOI: 10.1038/35041687
61. McEwen BS, 2002 Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. Neurobiol Aging 23: 921–939. DOI: 10.1016/S0197-4580(02)00027-1
62. Cals MJ, Succari M, Meneguzzer E, et al, 1997 Markers of oxidative stress in fit, health-conscious elderly people living in the Paris area. The Research Group on Ageing (GERBAP). Nutrition 13: 319–326. DOI: 10.1016/S0899-9007(97)83054-7
63. Kostka T, Drai J, Berthouze SE, Lacour JR, Bonnefoy M, 2000 Physical activity, aerobic capacity and selected markers of oxidative stress and the anti-oxidant defence system in healthy active elderly men. Clin Physiol 20: 185–190. DOI: 10.1046/j.1365-2281.2000.00245.x
64. Gidron Y, Russ K, Tissarchondou H, Warner J, 2006 The relation between psychological factors and DNA-damage: a critical review. Biol Psychol 72: 291–304. DOI: 10.1016/j.biopsycho.2005.11.011.