Psychological stress and aging: role of glucocorticoids (GCs)

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Abstract Psychological stress has extreme adverse consequences on health. However, the molecular mechanisms that mediate and accelerate the process of aging due to stress hormone are not well defined. This review has focused on diverse molecular paths that come out in response to chronic psychological stress via releasing of excessive glucocorticoids (GCs), involved in the aging process. GCs suppress transcription of nuclear cell adhesion molecules which impair synaptic plasticity, memory formation, and cognitive ability. Again, GCs promote muscle atrophy by means of motivating ubiquitin proteasome system and can repress muscle protein synthesis by inhibition of PI3-kinase/Akt pathway. GCs also inhibit interleukin-2 synthesis through suppressing T cell receptor signal that leads to loss of T cell activation, proliferation, and B-cell activation. Moreover, GCs increase the expression of collagenase-3, RANK ligand, and colony stimulating factor-1 that

induce bone resorption. In general, stress-induced GCs can play causal role for aging and age-related disorders.

Keywords Chronic psychological stress · Glucocorticoid · Glucocorticoid receptor · Aging

Introduction

Aging is not a disease (Aubert and Lansdorp 2008) but the progressive decline of cellular functions, accompanied by complex phenotypes and life-long amassing of random damages in somatic cells/tissues (Csermely and Söti 2006), which eventually results in mortality (Aubert and Lansdorp 2008). Among the many signs and symptoms, cognitive impairment (Hof and Morrison 2004), immune suppression (Kitajima et al. 1996), muscle atrophy (Schakman et al. 2009), and osteoporosis (Tamura et al. 2004) are some of the important features associated with aging (Nalla et al. 2004; Ager et al. 2006). Aubrey and de Grey (1999) defined aging as “deteriorative changes with time during post-maturational life that underlies an increasing vulnerability to challenges, thereby decreasing the ability of the organism to survive”. Regarding aging, numerous theories have been evolved to explain the phenomenon over the decades which are enlisted and briefly described in Box I. However, it is a common scenario that the metabolically tuned human body falls in an unpleasant state

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of emotional and physiological arousal provoked by environmental, psychological, or physiological stressors that he/she experiences in situations and perceives as threatening and risk to homeostasis (Sobhani et al. 2010). This event results from a long-term exposure of stimulus and precipitates a series of phenomena-activating physiologic responses which are generally non-adaptive and finally figured chronic state. In response to stress-like depression, anxiety; personality factors, social isolation, and sub-acute/chronic life stress etc. (Ho et al. 2010), hypothalamic–pituitary–adrenocortical axis (HPA) is stimulated to secrete glucocorticoids (GCs), a stress hormone (Slominski 2007) which play an important role in brain aging, suppression of immune system, and muscle protein degradation (Porter and Landfield 1998; Kitajima et al. 1996). Interestingly, the excessive release of GCs is encouraged by chronic psychological stresses that lead us to the highway of aging in which immune system, central nervous system, and endocrine system are influenced some how and concomitantly patronizing to get old (Ho et al. 2010).

Box I. Major theories explain the phenomenon of aging

Evolutionary theory: Mutated and normal genes which are not harmful at younger age could be deteriorating to late life (Weinert and Timiras 2003).

Molecular theory: Accumulation of somatic mutation, changes in gene expression, amassing of abnormal proteins due to lack of efficiency of protein-synthetic apparatus, and impairment of translation process cause aging (Weinert and Timiras 2003).

Neuroendocrine control theory: Alterations in neuroendocrine control of homeostasis results in aging-related physiological changes (Timiras 2007).

Free-radical theory: Aging occurs as a cost of cellular damages such as lipid (membrane), protein, and DNA damage due to high reactive free radicals that produced during oxidative metabolism (Weinert and Timiras 2003; Timiras 2007; Volonte and Galbiati 2009).

Telomere theory: Cells reach at senescent state due to loss of telomere during gradual replication (Weinert and Timiras 2003; Timiras 2007).

Perhaps, molecular mechanisms that arbitrate and hasten the process of aging due to psychological stress in relay of GCs are not well understood and frustrated many researchers for decades. Here, we are focusing on the role of GCs in the diverse molecular mechanisms in response to psychological stress that involved in aging and age-related disorders.

Stress and glucocorticoids

In stressful state, corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) are released from parvocellular neurons (Ströhle and Holsboer 2003) that project from the paraventricular nucleus to the median eminence (Samson et al. 2002). CRH and AVP travel from the hypothalamus via the hypophyseal–portal blood vessels to the anterior pituitary gland (Engelmann et al. 2004) where they act synergistically via type 1 CRH receptor and type 1b vasopressin receptor to trigger the release of adrenocorticotrophic hormone (ACTH) from the corticotrophs into the systemic circulation (Buckingham et al. 1996). In turn, ACTH acts on the adrenal cortex via type 2 melanocortin receptors to initiate the synthesis of glucocorticoids (Papadimitriou and Priftis 2009) 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 (Noorlander et al. 2006) through which the sequential release of CRH/AVP and ACTH from the hypothalamus and anterior pituitary gland is suppressed (Buckingham 2006).

Aging and hippocampal complex

Cognitive decline, one of the most common health-related worries, is governed by the hippocampal complex (Woodruff-Pak 1988). In the aged hippocampal complex, events like neurotransmitter and receptor alterations, dendritic alterations, decreased synaptic connections, decreases in average neuron size/number, and inhibition of long-term potency had been reported by McLay et al. 1997. Koivisto et al. (1995) estimated memory impairment in 76.4% and clinically defined age-associated memory impairment in 53.8% from studying of 1,049 Finnish individuals older than 60 years. Furthermore, age-associated cognitive impairment has been also found in vivo on rats and macaque monkeys (Hof and Morrison 2004). Recently, experiments on Sprague–Dawley rats by Lau et al. (2007) revealed that raised glucocorticoid secretion inhibits cell proliferation and neurogenesis in the hippocampus and found a causal relationship with depression. It is well-known that the adult brain possesses substantial plasticity in order to learn new

skills, establish new memories, and respond to injury throughout the life (Purves et al. 2004).

In vitro studies on nuclear cell adhesion molecules (NCAM) shows that presence of polysialic acid (PSA) on NCAM decreases NCAM-mediated cell adhesion and involves in the initial signaling events in synaptic plasticity (Ronn et al. 2000). In vivo study on rats by Hof and Morrison (2004) showed that the expression of PSA–NCAM is obvious for learning, and knockout mice study also demonstrated similar result (Murase and Schuman 1999). Furthermore, elimination of PSA from NCAM suggests that the balance between PSA–NCAM and NCAM is important factor for plasticity (Kiss et al. 2001). NCAM is considered to be a reliable marker of synaptic plasticity with its concentration reflecting the numbers of recently generated synapses. From this perspective, NCAM reductions would be regarded as a consequence of the structural changes. The specific reduction in the NCAM-140 isoform that was reported in chronically stressed rats which strongly indicates that glucocorticoid receptors (GRs) participate in the stress-induced modulation of cell adhesion molecules (Sandi 2004) via suppressing nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1). NF- κ B, a potential site of NCAM promoter has been detected in the postsynaptic density in cortical and hippocampal neurons and plays important roles in neuronal survival as well as in neuronal plasticity

(Simpson and Morris 2000). Transgenic mice with inhibited NF- κ B in forebrain neurons showed significant neurodegeneration by treatment with neurotoxic agents such as FeSO₄ and kainite in the hippocampal neurons, and knockout mice lacking p65 subunit of NF- κ B have a deficit in the spatial learning is well documented (Takeuchi and Fukunaga 2004). Therefore, NCAM reduction might reflect the decreased synaptic density that is induced by chronic stress.

Suppression of NCAM gene expression by GCs

GCs are lipophilic steroids thus can readily enter the neuron to interact with the intracellular GR (Huchison et al. 1993) results in conformational changes in the GR molecule and induces a poorly understood process known as receptor activation (Beato et al. 1995; Fig. 1). Downregulation of NF- κ B-driven NCAM genes result from an interaction between activated GR and p65 subunit of NF- κ B. Direct interaction between p65 and activated GR modifies or changes in p65 conformation that masks the activation domain(s) of p65 which result in down-regulation of NCAM genes transcription (Bosscher et al. 1997). In addition, a potential AP-1 recognition sequence is found very close to the apparent transcription start site on NCAM genes (Colwell et al.

Fig. 1 Suppression of NCAM expression by GCs. GCs triggers (+) GR to active state which negatively (–) regulated NF- κ B and AP-1, consequently blocking (X) NCAM gene expression instead of normal membrane receptor mediated signaling pathways

1992) which might also be repressed by GR (Datson et al. 2001). The inhibition of both AP-1 and NF- κ B activity has been demonstrated in vivo in the brain of rat (Vreugdenhil et al. 2001). The mechanism behind that is GR and AP-1 simply compete for a common coactivator complex containing CREB-binding protein (CBP) or p300. But it can only explain the transrepression of AP-1 activity by GR when the amount of CBP/p300 is limited. An interaction with the activated GR may induce AP-1 to recruit a corepressor complex instead of a coactivator (Karin and Chang 2001).

Aging and immune system

Aging is associated with the immunosenescence of most of the molecular machines of immune system (Graham et al. 2006) like dysregulation of inflammatory processes (Cesari et al. 2004), impaired wound healing due to diminish ability of macrophages to produce proinflammatory cytokines (Gomez et al. 2005), and decreased ability of T cells to respond when challenged with antigen, with large differences seen at age 60 and increasingly thereafter (Murasko et al. 1987). Another change seemingly inherent in normal aging is that B-lymphocytes impaired functionality with decrease in the antibody production (Castle 2000). One of the most conclusive evidence is in NK cells from the spleen and lymph nodes of older animals showed (in vitro) decreased immune functionality compared to younger rats (Graham et al. 2006).

Indeed, GCs have direct inhibitory actions on many inflammatory and structural cells involved in inflammation (Bhattacharyya et al. 2011). GCs slow down the release of inflammatory mediator's viz. secretion of chemokines and proinflammatory cytokines from alveolar macrophages in vitro (Barnes 1998) and in vivo in patients with asthma (John et al. 1998). In addition, GCs have a direct inhibitory effect on mediators released from eosinophils (Borish et al. 1992). GCs therapy increases apoptosis (Owen et al. 1987), contributes to slowdown eosinophil circulation, and reduces plasma concentrations of eosinophil cationic protein (Wempe et al. 1992) and cytokine production (Evans et al. 1993). Furthermore, GCs have an indirect inhibitory effect on mediators released from mast cells (Cohan et al. 1989) which

may be linked to the reduction in interleukin (IL)-3 and stem cell factor production. Mast cells can produce various cytokines (Kashiwakura et al. 2009), but whether those are inhibited by GCs is not yet certain.

GC-mediated T cell receptor signal inhibition

T cell activation, proliferation, survival, and release of lymphokines such as IL-2 and macrophage colony stimulating factor (GM-CSF; Hamilton 2008), which are likely to play an important role in the recruitment and survival of inflammatory cells but are very effectively inhibited by GCs (Barnes 1998). Here, we discuss the mechanism of the effects of GCs action in activated human CD4 T cells where T cell receptor (TCR) signaling pathway acts as a platform (Rentero et al. 2008; Fig. 2). It is well established that phosphorylation of lymphocyte-specific protein tyrosine kinase (Lck) and FYN, members of the sarcoma (SRC) family of nonreceptor tyrosine kinases, are proximal events in T cell activation (Palacios and Weiss 2004) and known to positively regulate the signaling initiated upon TCR stimulation through a variety of downstream pathways (Salmond et al. 2009). Conversely, reduced Lck and FYN kinase (a protein-tyrosine kinase) activities may have an important role in the fast immunosuppressive effects of GCs in immune cells (Stahna et al. 2007). In line with this notion, decreased activation of several signaling pathways downstream of the TCR upon dexamethasone (DEX; a synthetic GCs analog, inhibits Lck and FYN kinases in these immune cells) treatment has been observed, including suppression of PKB, PKC, ERK, JNK, and p38 MAPKs. The biochemical and functional responses to TCR ligands are largely determined by FYN-CD3 and Lck-CD4 associations. DEX treatment rapidly alters the cellular distribution of Lck and FYN which would likely result in decreased Lck/FYN kinase activities and suppressed TCR signaling (Löwenberg et al. 2005). TCR activation results in membrane translocation of Lck and FYN in an HSP90-dependent manner (Bijlmakers and Marsh 2000). Lck predominantly associates with CD 4 or CD 8 cell surface receptors (Artyomov et al. 2010) and FYN binds to CD3 coreceptors, resulting in Lck and FYN kinase activation (Lovatt et al. 2006). Once activated, Lck and

Fig. 2 Mechanism of immunosuppression of T cell activation by GCs. Schematic representation of TCR signaling process subdivided into two sides. Left sides present normal signaling through which IL-2 gene expressed. But, on right sides it is seen that GRs mediated TCR signaling where the intracellular membrane signal complex is negatively (–) regulated and consequently the tuned innermembranal complex loosening their relation results in TCR signal impairment, through this IL-2 gene expression is retarded (X)

FYN phosphorylate immune-receptor tyrosine-based activation motifs on the TCR, allowing downstream signal transduction to proliferate, differentiate T cells and consequently produce cytokines (Palacios and Weiss 2004). The classic mechanism of GCs action involves the GR and modulation of transcriptional and translational events (Rose et al. 2010). GR- and SRC-like kinases share a requirement for HSP90 for proper functioning, opening the possibility that GR act on Lck and FYN activities that are mediated by HSP90 (Nika et al. 2010). GCs cause disruption of TCR-associated multiprotein complexes containing GR, HSP90, Lck, and FYN, leading to reduce Lck/FYN enzymatic activities and impaired TCR signaling (Löwenberg et al. 2006).

Aging and muscle

The age-associated changes in body composition result from lower levels of anabolic hormones, neuromuscular alterations, decline in muscle protein synthesis, and a gradual/selective loss of muscle fibers (Bross et al. 1999). 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 (Welle et al. 1996). However, GCs inhibit protein synthesis in skeletal muscles (McGrath and Goldspink 1982) and stimulate muscle protein degradation (Kayali et al. 1987) which is responsible for muscle atrophy. The stimulatory effect of GCs on muscle proteolysis results from the activation of ubiquitin–

proteasome and lysosomal systems (Schakman et al. 2009). Increase in the components like ubiquitin, E2 enzyme, E3 enzyme, and 26S proteasome of the ubiquitin–proteasome pathway is synonymous with the activation of the pathway and interestingly, the ubiquitin–proteasome pathway is involved in the aging process muscles (Cai et al. 2004).

Inhibition of muscle protein synthesis by GCs

The Akt/PKB (serine/threonine protein kinase) signaling pathway is one of the prerequisite for muscle protein synthesis which consists of growth factor receptors, adapter proteins like insulin receptor

substrates (IRS), class I phosphatidylinositol 3-kinase (PI3K) and Akt/PKB kinases (Plas and Thompson 2005). Insulin-like growth factor I receptor (IGF1R) signaling can prevent apoptosis and induce muscle protein synthesis which is mediated by PI3K (Fig. 3). The binding of IGF1 or IGF2 with IGF1R trigger the receptor's intrinsic tyrosine kinase activities. Consequently, IRSs are phosphorylated (Tseng et al. 2002) and then interact with Src homology-2 domains of PI3K. Activated PI3K catalyzes the conversion of phosphatidylinositol 4, 5-bisphosphate to PIP3. After that, PIP3 binds to Pleckstrin homology domain of phosphatidylinositol-dependent kinase-1 which phosphorylates Thr308 residue on Akt (Mora et al. 2005). A further protective pathway

Fig. 3 Mechanism of muscle protein synthesis inhibition by GCs. Generally PI3K phosphorylates phosphatidylinositol 4, 5-bisphosphate (PIP2) to PIP3 which follow the Akt/PKB pathways for protein synthesis. But stress induced activated GRs negatively (–) regulate PI3K and block (X) the phosphorylation of PIP2. Consequently, the normal pathway falls down and depletion of protein synthesis

activated by Akt involves inhibition of GSK3 (glycogen synthase kinase-3) which results from its phosphorylation at an N-terminal serine residue (Ser21 in GSK3Alpha and Ser9 in GSK3Beta; Goll et al. 1991; Scheid and Woodgett 2001). Ultimately, GSK3 catalyses the phosphorylation and inhibition of eIF2B (eukaryotic protein synthesis initiation factor-2B), thereby inhibits protein synthesis. Hence IGF1R, by inhibiting GSK3, stimulates the de-phosphorylation and activation of eIF2B, contributing to an increased rate of protein synthesis (Senthil et al. 2002). In relax state, instead of bindings with eIF4G, eIF4E forms an inactive complex with any one of the eIF4E-binding

proteins (4EBP1, 4EBP2, or 4EBP3) and that is why translation is downregulated (Anthony et al. 2001). In activate stage, phosphorylated mammalian target of rapamycin (mTOR), a substrate for Akt, promotes signaling events to phosphorylate 4EBP to dissociate from eIF4E and result a marriage with eIF4G to activate eIF4F complex for promoting the initiation phase of protein translation by relieving 4EBP-mediated inhibition of eIF4E (Matsuo et al. 1997). At the moments of phosphorylation by mTOR, the ribosomal p70S6K and ribosomal protein-S6 becomes activated (Senthil et al. 2002) and that is required for biosynthesis of the cell's translational apparatus, a

Fig. 4 Protein degradation via UPS by GCs. Activated GRs positively (+) regulates and increases the activity of calpain, E2, E3 and 26S proteasome. As a results muscle proteins are degraded and ultimately fallout in muscle atrophy

critical component of cell growth and proliferation (Boylan et al. 2001). However, GCs can cause insulin resistance and leading to decrease PI3K activity in muscle (Saad et al. 1993) by activating the GR, showing the way to a competition with IRS-1 for association of PI3K subunits p110 and p85. The association of these subunits with the GR reduces IRS-1-associated PI3K (phosphorylation) activity and p-Akt (Hu et al. 2009).

Role of GCs in muscle protein degradation

Muscle tissue contains sarcoplasmic, myofibrillar, and stroma proteins (Tan et al. 1988). The role of the calpain in muscle protein degradation is likely to

involve principally the myofibrillar or the cytoskeletal proteins. Calpain rapidly cleaves titin, nebulin, and desmin that attach the Z-disk (Combaret et al. 2005) to release actin, myosin, and other polypeptide filaments (Goll et al. 1991). The released filaments can be reassembled or the polypeptide fragments produced by calpain degradation (Goll et al. 2008) and C-protein can be ubiquitinated and degraded to amino acids by the proteasome and cellular peptidases (Goll et al. 2003). Although calpain are unable to degrade actin and myosin, they seem to be involved in myofibrillar disassembly, with calpain-releasing myofibrils for degradation via ubiquitin–proteasome proteolytic pathway (Hasselgren et al. 2002; Fig. 4).

Through a two-step catalytic process, ubiquitin is activated by E1. ATP hydrolysis results in the

Fig. 5 Mechanism of GCs induced osteoporosis. The illustration represents two ways viz. bone resorption and bone matrix break down as a process for osteoporosis. Here, activated GRs positively (+) regulated MMP-13 and increased ejection of collagenase 3 which is responsible for bone matrix break down. On the other side, RANKL and MCSF positively (+) regulated and OPG is negatively (−) regulated by GRs. The both regulation induce bone resorption

formation of acyl-adenylate intermediate linking AMP with the carboxy-terminal carboxyl group of glycine in ubiquitin. This adenylated carbonyl group then forms a thioester linkage with a cysteine residue of E1 (Lecker et al. 1999). The activated ubiquitin unit is subsequently shifted to the active site cysteine of a second enzyme E2 which can recognize E3 that determine the specificity of substrate ubiquitylation (Ravid and Hochstrasser 2008), and catalyze the transfer of ubiquitin from the E2 thioester intermediate to an isopeptide linkage with a selected substrate (Lecker et al. 1999). Progressive rounds of E3-promoted ubiquitin ligation result in the attachment of a polyubiquitin chain to the substrate (Bodine et al. 2001). Proteins tagged with polyubiquitin chains are recognized for degradation into small peptides by the 20S proteasome where the proteolytic sites lay on inner surface of the β rings and found three types of proteolytic activity: chymotrypsin-like, trypsin-like, and caspase-like that work together to catalyze the complete digestion of proteins (Orlowski and Wilk 2003). Calpastatin is an endogenous specific inhibitor protein for calpain present in almost all mammals (Murachia 1983; Sato et al. 2011), and having the property of trimming down its mRNA concentrations if treated with DEX (Yeh et al. 1994). The stimulatory effect of GCs on muscle proteolysis results from the activation of ubiquitin proteasome system (UPS; Tisdale 2005), cathepsins, and calpain. GCs stimulate expression level of several components of the UPS

either E2, E3 or proteasome (Schakman et al. 2008) which are guilty for protein degradation.

Effect of GCs on bone resorption

Age-related changes in mesenchymal stem cells include increases in senescent cells, loss of differentiation and proliferation potential, and loss of bone formation (Stolzing et al. 2008). The cell populations of bone osteoblasts and osteoclasts that participate in remodeling process are derived from different progenitor (Robling et al. 2006). The osteoblasts derive from mesenchymal stem cells are found in the bone marrow, periosteum, and soft tissues. They deposit osteoid and mineralize it; forming new bone (Lian and Stein 2001) involves spatiotemporal coordination of interaction among diverse endocrine, paracrine, and autocrine factors (Datta et al. 2008). For osteoclastogenesis, the TNF-related cytokine RANK ligand (RANKL) and the polypeptide growth factor CSF-1 are necessitated (Boyle et al. 2003) to induce expression of genes that characterize the osteoclast lineage, together with those encoding tartrate-resistant acid phosphatase (TRAP), cathepsin K (CATK), calcitonin receptor, and the β_3 -integrin, guiding to the development of mature osteoclasts (Lacey et al. 1998).

Acidification by secretion of protons directs to activate TRAP and CATK, which are responsible for

Fig. 6 An overview of the role of chronic psychological stress leading to aging

the degradation of bone mineral and collagen matrices (Boyle et al. 2003). RANKL binds with RANKL-like osteoprotegerin (OPG; Khosla 2001) instead of receptor activator of NF- κ B (RANK; Anderson et al. 1997) and neutralize RANKL to regulate both osteoclastogenesis and activation of mature osteoclasts negatively (Boyle et al. 2003). Collagenase 3 (MMP-13) secreted by human osteoblasts, the human chondrocytes that degrades type I collagen fibrils, is the major component of the bone matrix. Figure 5 shows that GCs trigger GCs-dependent cytosolic proteins that join to a selected area of the 3' untranslated region of the collagenase 3 RNA to modulate the stability of other mRNAs and prolonged the half-life (Canalis and Delany 2002). GCs increase the expression of RANKL and decrease the expression of OPG at mRNA levels in stromal and osteoblastic cells lineage (Hofbauer et al. 1999). Contrarily, GCs also enhance the expression of CSF-1 that induces osteoclastogenesis in presence of RANKL (Rubin et al. 1998). GCs have a direct inhibitory effect on osteoblasts mediated by three routes (Weinstein et al. 1998): (1) inhibition of the replication of osteoblastic lineage, (2) a decrease in the genesis of new osteoblastic cells, and (3) induction of osteoblastic cell death and/or apoptosis (Doga et al. 2004).

Summary

In response to psychological stress, hypothalamus secretes CRH and stimulates pituitary to emit ACTH which is transported to adrenal glands to release GCs for exerting numerous metabolic effects to contribute aging (Fig. 6). The hippocampus is more vulnerable due to the presence of highest density of GRs resulting GCs-mediated transcription-suppression of NCAM via the inhibition of NF- κ B and AP-1. Activated GRs dissociates TCR linked multiprotein complex through which TCR-signaling is suppressed. As a consequence T cell activation, T cell proliferation and B-cell activation are impaired. Again, GCs-induced muscle atrophy by means of UPS is characterized by reduced myofibrillar protein content. The stimulation of UPS by GCs is mediated through the increased expression of atrogin-1 and MuRF-1 which encode two ubiquitin ligases those involved in the target protein degradation. Participation of calpain

causes myofibrillar disaggregation and release of myofibrils for degradation by the ubiquitin-proteasome proteolytic pathway. Calpastatin inhibits calpain and GCs reduce calpastatin to facilitate calpain's proteolytic activities. GCs also exert an anti-anabolic action by blunting muscle protein synthesis which may result from changes in the IGF-I-induced signal transduction through the inhibition of PI3-kinase/Akt pathway. Moreover, GCs amplify expression of collagenase 3 (MMP-13) that degrades type I collagen fibrils, the major component of the bone matrix. Furthermore, GCs enhance CSF-1 expression to induce osteoclastogenesis in the presence of RANKL. As a result, bone mass is reduced with a consequent increase in bone fragility and susceptibility to fracture and eventually osteoporosis occurred; in turn, that is a part of aging process. From the overall studies, it can be concluded that the chronic psychological stress has deteriorating effects on most of the tissues of the body and contribute in the acceleration of aging (Fig. 6).

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