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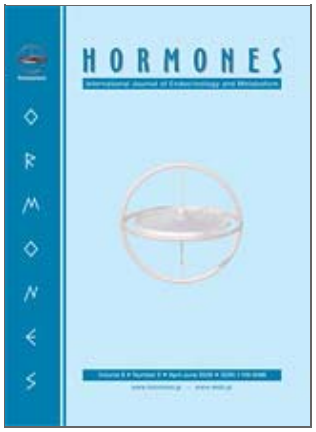

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Review

Psychological and metabolic stress: A recipe for accelerated cellular aging?

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Abstract

Chronic stress can affect human health through a myriad of behavioral and biochemical pathways. This review focuses on some key hormonal and metabolic pathways that appear important today. 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 effects. 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 conducive to several cell aging mechanisms, mainly dampening telomerase and leading to telomere length (TL) shortening and cell senescence. Immune cell telomere shortness is linked with many chronic disease states 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 interventions for interrupting the stress-aging cascade are discussed.

Keywords

Cortisol, Insulin, Obesity, Oxidative stress, Psychological stress, Telomerase, Telomere Length

A. INTRODUCTION

Chronological age is the best predictor of chronic diseases. The elderly population (65 and older) is projected to increase significantly, reaching 72 million in the United States by 2030.[1]

Since the burden of diseases of aging on the healthcare system will likely be overwhelming, it is important to gain a deeper understanding of biological aging. The development of age-related diseases occurs at different rates in different individuals, and psychological distress appears to be an important factor promoting earlier onset of age-related diseases.[2-6] Thus, better understanding of how stress is likely to promote "biological aging" may lead to clinical interventions or policies that could have a broad public health impact.

Below is a selective review of some of the major effects of chronic stress on metabolism and cell aging. It demonstrates how a stress-induced anabolic/catabolic imbalance—characterized in part by high cortisol, glucose, and 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 together they promote energy storage in abdominal fat tissue. This body habitus is associated with systemic inflammation and oxidative stress which in turn affects cell metabolism and can accelerate cellular aging, possibly affecting autophagy, sirtuins, and telomere maintenance. The review concludes with the thesis that chronic stress-induced biochemical imbalance, the direct central effects and indirect effects from adiposity, promote leukocyte cellular aging, as shown in Figure 1. Although the figure shows linear relationships in a closed system for simplicity, cell aging is just one of many outcomes of stress, and likewise stress is just one of many factors affecting cell aging.

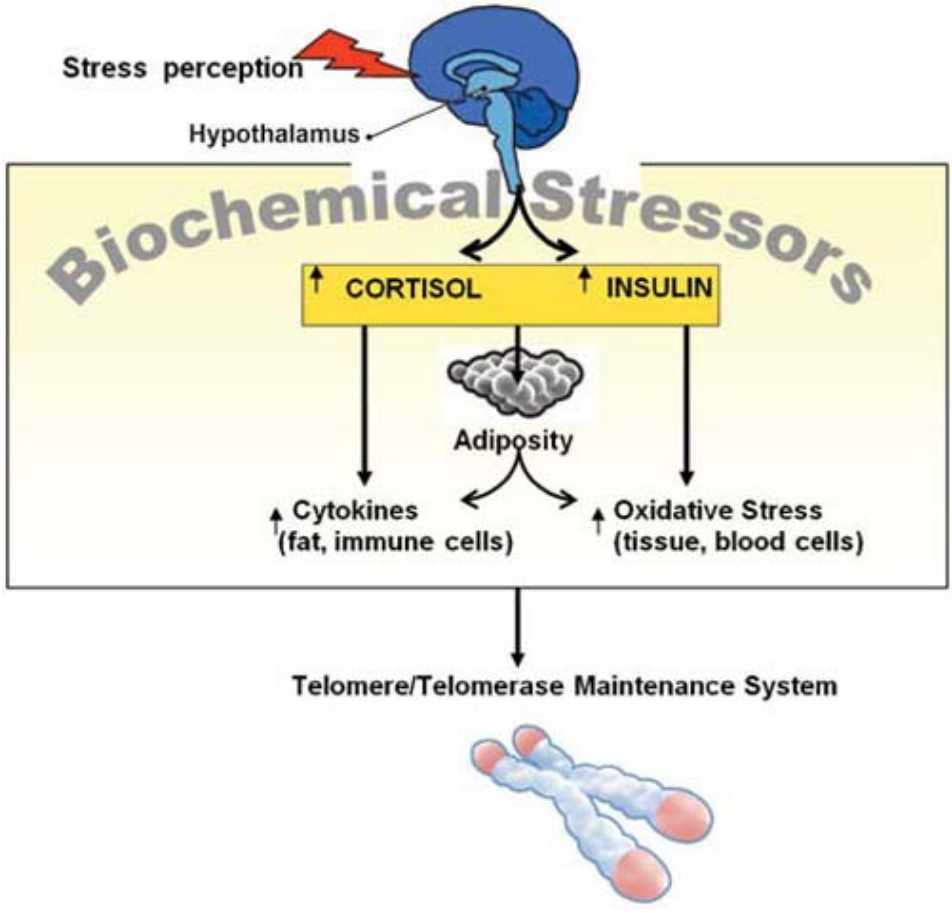

Figure 1. Some systemic and cellular effects of chronic stress

B. METABOLIC MECHANISMS OF AGING

B.1. 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.[7] 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, all aiming at genome protection (See Section D).

Efficient allostasis describes facile adaptation, such as a quick peak stress response to mount energy to an acute stressor, and a rapid return to baseline, when the stressor terminates. Impaired allostasis is characterized by exaggerated reactivity peaks and sluggish recovery.[4,8] Chronological aging impairs an organism's ability to sustain efficient allostasis when responding to different stressors. In humans, this is well-demonstrated by examining physiological regulation such as dynamic hypothalamic-pituitary-adrenal (HPA) axis responses or temperature changes. The cortisol response to stressors can be exaggerated in the elderly, and additionally, there is a sluggish negative feedback, so that cortisol stays elevated longer.[9,10] Aging also causes a greater operating range of temperature, making the elderly more vulnerable to heat shock when under heat stress. Thus, impaired allostasis is inherent in chronological aging.

Chronic stress causes certain regulatory systems 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 androgens and IGF-1. An index of these markers is commonly used as a way to measure "allostatic load," the damage due to repeated fluctuations of the stress response. A high allostatic load index, indicating altered set points, has been linked to earlier mortality.[11] Here we focus on four of these factors—cortisol and insulin, inflammatory factors, and oxidative stress—labeling these 'biochemical stressors'. These factors that are stress responsive become imbalanced during chronic stress, acting as physiological stressors which can accelerate cellular and tissue aging.

B.2. The anabolic/catabolic hormonal balance

Chronic stress tends to shift the hormonal balance toward low levels of the anabolic hormones that promote growth of lean and skeletal mass and prevent adiposity, such as androgens and IGF-1. 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).[12] In addition, cortisol increases insulin levels.[13,14] 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 (See B2, below), 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 impaired negative feedback of the HPA axis, to slower recovery from stressors, and to either higher or lower cortisol levels.[3,4] A considerable body of research has linked depression and chronic stress to elevated stress hormones, mainly cortisol and catecholamines,[3,15-17] though not in all cases.[18-20] While around 40% of depression is characterized by high cortisol levels, both depression and chronic stress have also been linked to hypocortisolemia or low Corticotropin-Releasing Hormone (CRH).[21,22] In particular, atypical depression, states of chronic fatigue, and post-traumatic stress syndrome are linked to profiles of low cortisol and/or enhanced HPA axis negative feedback.[21,23] It may be that a deficiency of

cortisol contributes functionally to symptoms of inflammation and fatigue. Further, hypercortisolemic depression may actually promote functional hypocortisolemia, since glucocorticoid receptor sensitivity is low, which can lead to glucorticoid resistance and impaired signaling.[24] Here we focus on effects of high cortisol, but acknowledge that low cortisol may have effects on cell aging through alternative pathways.

Anabolic hormones including androgens [Dehydroepiandrosterone (DHEA), and testosterone] and the 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 men, but higher incidence in women.[25-27]
Like aging, chronic stress can lead to decreased IGF-1, GH, DHEA, and testosterone levels,[12,28] although there are exceptions to this.[29] 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.[30]

DHEA often serves as an antiglucocorticoid and can buffer effects of inflammation and oxidative stress.[31] Therefore, deficits in anabolic hormones may in some cases leave actions of cortisol unopposed. Anabolic hormones at sufficient levels signify restorative processes, 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).[32,33] Low levels of testosterone predicted mortality in male veterans.[34] Another study examined whether low levels of IGF-1, testosterone, and DHEA were related to earlier mortality in men, while adjusting for various behavioral factors as well as presence of chronic diseases. They found that being low on all three of these hormones was related to a 2.5 times higher risk of early mortality.[35]

GH and IGF-1 decrease with aging, a phenomenon associated with muscle atrophy, but anabolic hormones, also promote malignancy such as breast cancer.[36] 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.[37] Thus, growth factors are double-edged swords: they have favorable effects on musculoskeletal and thus metabolic health, yet increase the risk of cancers. Despite these links between GH/IGF-1 and good metabolic health in humans, GH/IGF hormones are linked to shorter lifespan in most lower species and mammalian models.[38] New research on genetic variation of genes controlling the IGF-1/GH signaling pathway, such as the FOXO gene, support the animal studies showing that mutations in these signaling pathways are linked to longevity in humans as well,[39] painting a complex picture of the role of these growth hormones in human health.

B.3. Insulin resistance and adiposity

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.[40]

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.[41-45] For example, psychological stress, including job stress, is associated with abdominal fat in cross-

sectional [46] and prospective studies.[47-49]

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.[50] Visceral fat is well equipped to respond to the stress-induced combination of high cortisol and high insulin. For one, it has a greater density of glucocorticoid receptors.[51,52] 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.[53] 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.[54]

In turn, abdominal fat contributes to numerous biochemical stressors. Clinically, greater abdominal fat thickness is associated with higher levels of systemic total oxidative stress (lower antioxidants, higher lipid markers)[56] and greater number of inflammatory markers.[57] Fat cells, both subcutaneous, abdominal and particularly visceral abdominal fat, release cytokines such as TNF-a and IL-6.[58] Monocytes infiltrate the fat, especially near dead cells, and further release cytokines, promoting systemic inflammation. Animals with fat transplants of visceral but not subcutaneous origin develop increased inflammatory and cardiovascular disease, suggesting that the inflammation alone is pathogenic.[55] Thus, the visceral fat tissue is a likely source of the chemicals that induce cellular aging.

B.4. Oxidative stress

Production of free radicals (oxidative stress) is thought to exert a major influence on cell aging and tissue damage,[59,60] particularly to cardiac cells and the brain.[61] 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 young adults,[62] or at least comparable to antioxidant defenses,[63] suggesting that oxidation is not inevitable in aging. It appears that psychological stress and lifestyle factors such as smoking and sedentariness have an impact on the level of oxidation.[64,65] Oxidation in turn is 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 poorer cognitive function, loss of autonomy, loss of ability to perform daily activities, and institutionalization, as well as depressive symptoms.[66]

Oxidative stress appears to play an especially important role in the 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.[67,68] DHEA and estrogens can prevent oxidative stress damage in neurons.[69-71] DHEA can block cortisol-mediated excitatory neurotoxicity, pointing to the likely importance of the balance between cortisol and DHEA.[71]
There are a growing number of studies both in rats[72] and in humans[73-76] that have found links between markers of oxidative stress and psychological distress. Markers of oxidative stress are increased by acute stress exposure[77,78] as well as by chronic states, such as major depression[79] and duration of exposure to caregiving.[76] In one study of acute stress, individuals who responded with higher ratings of anger and tendency to suppress anger had greater reactive oxygen species 30 minutes after the acute stressor.[77] However, other studies found that acute

stress may reduce markers of oxidation. It may be that both the state of a person's health and antioxidant defenses together determine 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. Elevations of glucose and insulin from chronic stress may promote free radical production through auto-oxidative glycosylation and through insulin-mediated sympathetic activity.[80]

C. HEALTH BEHAVIORS

C.1. 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.[81-83] 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.[64]

C.2. Eating behavior has highly significant effects on biochemical stressors (oxidative stress and inflammation). Overeating can lead to increased aerobic metabolism and thus overproduction of free radicals and increased fat storage. Excess adiposity in turn can lead to decreased insulin sensitivity. An excess glucose infusion, possibly analogous to a binge episode of overfeeding, led to a decrease in antioxidants, increase in liver oxidative stress, and systemic inflammatory response.[84] In a rat model of metabolic syndrome, high fat and sugar feeding leads to greater oxidative stress,[84,85] apparently through upregulation of NAD(P)H oxidase in kidney and cardiovascular tissue, and downregulation of antioxidants. Dietary fat can decrease the activity of PPAR-γ, which has anti-inflammatory action. PPAR-γ inhibits proinflammatory cytokines in monocytes, partly through inhibition of nuclear factor kappa B (NFkB). In one study of patients with metabolic syndrome, exposure to dietary fat overload led to lower expression of PPAR-γ, and such decreases in turn were correlated with greater oxidative stress.[86] In another study in rodents, a thiozolidinedione, an agonist of PPAR-γ, used to increase insulin sensitivity, also reduced oxidative stress (and visceral fat).[84] Caloric restriction can also reduce oxidative stress, as described below (Section F.2).

While actual caloric restriction has many positive effects on biochemical milieu, self reports of cognitive dietary restraint (trying to restrict calories, but not necessarily doing so) appear to show different or even opposite relations. Dietary restraint, especially in combination with a strong tendency to overeat, is related to higher cortisol levels[87] and, in some studies, to perceived stress.[88] Restraint is also related to shorter leukocyte telomeres, independent of body mass index.[89] The association could be due to a myriad of factors related to restraint. We speculate that restraint might be a proxy factor for greater exposure to both psychological and metabolic stress, including high cortisol and bouts of caloric restriction, followed by overeating and the ensuing biochemical stress described above.[89]

Many studies try to covary out health behaviors to examine pure effects of stress arousal. However, stress works both directly and also through behavioral pathways. Chronic stress serves as an organizing factor, shaping most daily self-care behaviors and sleep. For example, chronic stress or cortisol exposure motivates people to select high fat food and to overeat.[90,91] Chronic stress impairs sleep, and short duration sleep is a predictor of weight gain.92 Thus,

while it is helpful to examine 'unique' effects of chronic stress on physiology, the phenotypic effects inherently include several of these behavioral pathways. In the next section we review how stress induced biochemical changes may be related to several cell aging mechanisms.

D. CELL AGING MECHANISMS

D.1. The Telomere/Telomerase Maintenance System

The telomere/telomerase maintenance system, discovered by Elizabeth Blackburn, Carol Greider, and colleagues, offers insight into how cells age and senesce and, as recent research suggests, how people grow 'old' biologically. Telomeres are the protective nucleoprotein structures capping the ends of eukaryotic chromosomes, consisting of a simple repeat sequence (TTAGGG). Telomeres naturally shorten with mitosis. With every cell division, a portion of the telomeric DNA may not be replicated due to the "end replication problem"—that is, DNA polymerase does not work properly at the end of a DNA strand.[93] Thus, older mitotic cells tend to have shorter TL than younger cells. TL shortening is not merely a marker of cellular aging but also a mechanism, with important functional consequences. Mitotic cells can undergo a limited number of cell divisions before they become senescent and lose the ability to grow and divide, unless there are other conditions, such as high telomerase, as explained below. Telomere shortening is a mechanism for the development of this cellular senescence. Short TL leads to genomic instability, end-to-end chromosome fusion, less efficient mitosis, and loss of ability for cell replenishment.[94-96]

Telomerase provides enzymatic maintenance of TL and can counteract shortening and its functional consequences. Telomerase is a ribonucleoprotein reverse transcriptase cellular enzyme that adds telomeric DNA to shortened telomeres. If the TL shortening represents the clock ticking forward on the cells limited lifespan, telomerase can reverse or slow this clock.[97] Short TL stimulates telomerase, and cells with short TL can be stable with sufficient telomerase. Thus, TL and telomerase form an intricately interdependent dynamic system. Telomerase may also have independent effects on organismic health by, for example, promoting cell longevity even in the face of critically shortened telomeres.[97]

Shortened telomeres are linked to age-related disease and mortality. Shorter TL is associated with CVD[98,99] and risk factors including pulse pressure,[100-102] obesity,[104] insulin resistance,[103] and diabetes.[104-106] Shorter TL predicts mortality in non-clinical samples,107,108 as well as in samples with chronic kidney disease,109 Alzheimer's,[110] and stroke.[111]

D.2. Biochemical stressors affect the Telomere/Telomerase maintenance system

Stress arousal appears to be linked to telomerase and TL maintenance. Two studies have examined stress hormones, finding that cortisol is associated with shorter TL in vivo112 and that exposure to cortisol dampens telomerase activity in vitro.[113] Markers of inflammation are linked to TL shortening in several studies. Shorter TL length has been related to higher IL-6 and CRP in hemodialysis patients,[109] and in men.[108] Certain inflammatory factors can lead to T cell turnover, and possible TL shortening, if in the presence of low telomerase.

Oxidative stress clearly exerts a negative influence on TL maintenance. It can dramatically decrease TERT (telomerase protein) activity[114,115] and can damage telomeric DNA much more than non-telomeric chromosomal DNA of fibroblasts in vitro.[116] Conversely, addition of

antioxidants decelerates TL shortening in cultured cells[117] and prolongs telomerase activity.[118] Cross-sectional research in humans is consistent with the concept that oxidative stress may have cumulative effects on TL length. We found that oxidative stress imbalance (ratio of oxidative stress to antioxidants) in vivo is associated with shorter TL length,[76] and others have now found similar associations using various markers of oxidative stress.[119-121]

Insulin Resistance and adiposity

TL length is related to many factors associated with overeating, among them excess adiposity, insulin resistance, and increased leptin levels.[104] In one study, an increase in obesity over ten years was associated with a decrease in TL length.[103] Multivariate modeling suggested that this was due to insulin resistance. Similarly, another study found that hypertension was associated with shorter TL, also accounted for by insulin resistance.[121] A recent cross-sectional study found the longest TL in healthy controls, and progressively shorter TL length in people with impaired glucose tolerance and diabetes without plaques, and the shortest in those with diabetes and plaques.[120] Another study found that within diabetics, oxidative stress and not inflammation was correlated with monocyte TL length. Most participants were taking statins, which can reduce inflammation and might explain the null finding with inflammation.[106]

Thus, one can speculate that chronic caloric excess may be an early proximal promoter of accelerated aging through its effects at the systems level on body composition and insulin sensitivity, and at the cellular level through affecting the telomere/telomerase maintenance system.

D.3. Additional putative pathways of psychological stress that affect cell aging

Stress resistance

Although no studies have examined effects of psychological stress on cell aging mechanisms, there is a solid body of research examining effects of physiological stressors. Excessive exposure to physiological stressors can cause damage to molecules, necessitating the mobilization of cell repair mechanisms, promotion of housekeeping activities, and recovery from the stressor.[122] When these protective functions are overwhelmed, damage ensues. Several examples of stress and damage were reviewed above, such as the effect of oxidative stress on TL shortening.[123]

However, more intriguing than stress-induced damage is stress induced resistance. Small doses of physiological stressors can promote longer living cells. Short-term manageable stressors can promote “hormesis” or a toughening of the cell.[124] All organisms from c. elegans to humans have intracellular stress responses that increase when exposed to stressors and that protect them from physiological stressors such as heat and ultraviolet radiation. These protective responses to stress have been labeled ‘stress resistance.’ This includes energy metabolism, heat shock proteins, DNA repair enzymes, and free radical scavengers.[125,126] These are crucial for cell and organism survival. For example, heat stress can denature proteins and cause them to aggregate. Heat shock proteins serve as molecular chaperones for the damaged molecules.

Stress resistance is affected by both the dose of the stressor and cell’s age and is thought to be a major pathway promoting cell longevity.[127] For example, mild heat treatments early in life produce greater heat shock proteins and longevity in c. elegans.[128]

Stress resistance appears to involve energy regulating and growth signaling pathways. Old cells

cannot generate energy as efficiently, possibly due to aged mitochondria. Aging impacts the ability to respond to stressors. Cells of older people have poorer response to physiological stressors,129 including lower heat shock protein response. In one study, immune cells from an elderly sample exposed to paraquat had an 8% mean increase in antioxidant response (superoxide dismutase or SOD), whereas those under 40 years had an 80% response. Of the almost 50% who died five years later, all showed a low SOD response to stress.130 Even though this was a small sample, it demonstrates the effect of chronological aging on stress resistance and offers a link between resistance and longevity in humans.

Activity of the somatotropic axis is also related to stress resistance. Cells (fibroblasts) from long-lived animals, such as the Snell mice which have low IGF, show stress resistance to injuries from oxidative stressors. Long-lived mutant worms, which have low activity in the insulin/IGF signaling pathway, have greater stress resistance to heat stress and oxidative stress.[124] Stress resistance is a common characteristic of certain long-lived mutant animals,[131] although in several cases mechanisms promoting stress resistance can be uncoupled from those promoting longevity.[132]

Biochemical stressors are linked to other cell aging mechanisms

There are several cell aging processes that are particularly affected by excess energy balance—among them systemic over-exposure to glucose and insulin. Excess glucose is a key factor that is pro-aging through both direct and indirect effects of insulin exposure.[133] There are numerous ways in which excess glucose and insulin can lead to cellular aging, as reviewed by Kassi et al.[133] For example, glucose and increased glycolysis can decrease sirtuins and autophagy.

Sirtuins, protein deacetylases, are important for stabilizing DNA and for longevity. They appear to reduce inflammation and oxidative stress, to promote stress resistance,[134] and may promote stability of the telomere.[135] No studies have examined whether stress mediators such as cortisol and catecholamines affect expression of sirtuins.

Autophagy, the breaking down and recycling of damaged molecules, is an important housekeeping function of the cell. It thus allows cells to adapt to their changing environment and might be thought of as a key player in allostasis of the cell. Autophagy, or 'self-eating', occurs by enzymatic degradation of intracellular 'garbage.' Autophagy becomes impaired with aging, and low levels of autophagy are related to cancer and neurodegenerative diseases.[136] Systemic regulators of autophagy are not well studied. However, caloric restriction promotes autophagy, which in turn is required for the caloric restriction-induced longevity in c. elegans.[137] Insulin may also regulate rate of autophagy. High levels of circulating insulin can impair autophagy in the kidney,[138] whereas decreased insulin receptor signaling promotes autophagy.[139] Several studies suggest that acute exposure to stressors or glucocorticoids appears to increase autophagy, but no studies have examined the effects of chronic stress exposure.[140,141]

E. INDIVIDUAL DIFFERENCES: WHO WILL SUFFER ACCELERATED AGING FROM CHRONIC STRESS EXPOSURE?

We have discussed chronic stressors as relevant triggers of a stress cascade of cellular aging, focusing on leukocyte TL. Stressors can lead to a wide range of emotional responses, such as anger, fear, or sadness and withdrawal, and each of these likely has their own physiological profiles. Individual temperament and these distinct emotional responses to chronic stressors will influence the stress signatures—the type of stress responses and potential dysregulation that one encounters. Therefore, it is important not only to identify groups at greatest risk of exposure to

chronic stressors but also to phenotype who within these groups are most vulnerable to the stress cascade. Thus, we briefly define the psychological stress response that appears to be most relevant to our model. In this model, the typical chronic stress response is characterized by exaggerated levels of high cortisol and high insulin.

Who is at most risk of this type of stress response? In animal studies, anxiety proneness is linked to greater reactivity, which in turn is linked to aging. For example, in rats, freezing or slower maze performance predicts a premature aging syndrome, cognitive decline, lower antioxidants, and higher oxidative stress.[142,143] Further, greater behavioral reactivity or arousal is linked to shorter lifespan.[143] From an evolutionary perspective, anxiety prone individuals, those who tend to vigilantly monitor the environment, should do well in times of acute stress, but when exposed to chronic stress, the common condition in modern society, she or he will suffer from greater levels of allostatic load than other types of responders, such as those responding with anger rather than fear and anxiety.[144]

While there is no 'one to one' mapping of personality onto stress response, in general, the exaggerated cortisol response appears to be most typical of people with a cognitive style characteristic of greater trait anxiety. Below we discuss several key traits related to anxiety, specifically greater social inhibition and vulnerability to social evaluative threat. Social evaluative threats elicit strong cortisol response.[145] People with a more inhibited personality type, characterized by anxiety or low self-esteem, are prone to high cortisol reactivity or lack of cortisol habituation over time[146] and have higher activation in their amygdala in response to novel or stressful stimuli.[147,148] Many studies have found that people with the 'distressed' personality —characterized by negative affect/neuroticism and social inhibition (suppressing expression of negative feelings)—tend to have greater proinflammatory cytokines as well as increased cardiovascular morbidity and mortality.[149,150] In the first study examining a personality trait and telomere length, O'Donovan et al found that pessimism, the tendency to expect negative outcomes in the future, was related to shorter telomere length, as well as greater IL-6.[151]

Social and genetic contexts will also affect relationships between personality and stress related aging. Those with high social support tended to show lower cortisol reactivity and neural threat responses to a social evaluative stressor.[152] People with the short allele of the serotonin transporter, which is related to higher neuroticism, and exposure to greater life stress, tend to have higher activity in the amygdala during a resting baseline when their mind is not occupied by tasks.[153] It is likely that personality marked by stress vulnerability or stressor exposure alone will only be weakly predictive of stress related aging. Rather, gene-environment interactions will be important to predict meaningful variance in stress-induced aging.

F. INTERVENTIONS: CAN WE REVERSE OR AMELIORATE METABOLIC AGING?

Can interventions improve biochemical stressors? This question has been addressed in many types of studies so far, including pharmacological, psychological/behavioral, and caloric restriction studies. Improved A/C balance (decreased in cortisol, insulin, and increased in DHEA) can be partly achieved by behavioral interventions that work directly on stress and metabolic pathways, targeting neural regulation of these pathways.

F.1. Psychological/Behavioral interventions

By reducing perceptions of stress and increasing healthy behaviors, we may promote subtle but

important improvements in A/C balance, reducing cortisol and increasing anabolic hormones, vagal tone, and other restorative processes. Furthermore, by restoring hormonal balance naturally, through increasing endogenous secretion (vs. pharmacologically), one preserves the secretory patterns and diurnal rhythms (vs. a bolus at one time of day, as in most pharmacological approaches). These changes in hormonal milieu may in turn slow cell aging processes.

Interventions that include health behavior change in addition to psychosocial support or coping skills are likely to be more effective in improving health than targeting only one behavior. Increasing fitness is likely one of the most potent interventions for restoring A/C balance and can improve well-being. Long-term exercise can decrease cortisol and increase DHEA, GH, and IGF-1,[154] and is associated with reduced cortisol reactivity[155] and cardiovascular reactivity to acute stress,[156] as well as reduced anxiety[157] and depressive symptoms.[158]

Psychosocial interventions have been effective in improving A/C balance.[159] For example, an enrichment program for elderly subjects[160] increased DHEA, testosterone, estradiol, and GH levels, as well as significantly attenuating decreases in height, likely indicating less bone loss. In addition, Cruess and colleagues have shown that a cognitive behavioral stress management, designed to reduce stress appraisals and depressive symptoms, can improve A/C balance by reducing cortisol and catecholamines and by increasing DHEA and testosterone.[161] A yoga intervention for women with breast cancer appeared to slightly attenuate the post-radiation damage to DNA, compared to a control group of women receiving supportive counseling.[162]

Nutritional interventions are a potent way to improve biochemical milieu and possibly cellular aging. A low fat diet for type 2 diabetics can reduce adiposity, insulin resistance, oxidative stress, and inflammatory factors.[163] Combining improved diet with stress reduction and activity may provide the most potent interventions for healthy aging. A preliminary intervention study of intensive lifestyle modification across these domains found significant increases in telomerase.[164] Currently, our research group at UCSF is developing interventions that focus on reducing metabolic and stress arousal pathways (including mindful eating behavior, improved nutrition, activity, and stress reduction). However, one limitation to most behavioral interventions is poor long-term maintenance of behavioral changes, such as low compliance with effective doses of daily meditation, healthy diet and activity. The biochemical changes reviewed may last only as long as there is sufficient maintenance of the behavioral and psychological changes.

F.2. Caloric Restriction

Caloric Restriction is one of the most reliable manipulations to increase lifespan across species, and the complex mechanisms are reviewed elsewhere.[165,166] Caloric restriction appears to decrease metabolic rate, free radical generation, adiposity, and sympathetic activity and may reduce insulin and increase insulin sensitivity and DHEA-S levels.[167,168] It is thought that caloric restriction increases longevity in part through suppressing expression of sirtuins which then indirectly suppress fat mobilization (through suppressing PPAR-γ).[169]

Thus, caloric restriction appears to reduce biochemical stressors and the stress cascade described in Figure 1, with one important exception. It is notable that it appears to increase cortisol, despite having overwhelmingly positive effects on health. No studies have yet examined whether caloric restriction actually increases telomerase activity or TL length.

SUMMARY

There is now a large body of support for metabolic changes during psychological stress, toward energy storage in abdominal fat depots, and away from restorative activities of the anabolic hormones.[170] Although there are few studies examining psychological stress and cell aging, Figure 1 proposes the hypothesis that stress related biochemical factors (hormones, inflammatory factors, and oxidative stress) may promote cellular aging, particularly by dampening telomerase and leading to earlier cell senescence. Like chronic stress, abdominal obesity may systemically affect cell aging through a similar cascade of biochemical stressors—mainly insulin and glucose, and inflammation from fat tissue. Together, stress and obesity could powerfully fuel a state of biochemical stress and thus be a recipe or pathway for accelerated cell aging. Given the preponderance of psychological stress and its effects on food consumption and abdominal obesity, a better understanding of the interaction between stress and obesity may offer ways of preventing the biochemical stressor cascade.

Several studies have linked the systemic changes in hormonal balance and adiposity with cell aging. Most of these studies have been correlational clinical studies and do not demonstrate causal pathways. More mechanistic studies, using animal and in vitro models, need to be performed in order to test whether these correlations represent causal relationships. Given that the systemic responses of the nervous system are regulated by psychological appraisal processes, the prefrontal cortex and limbic system, psychological stress resistance must also be considered a key determinant of stress arousal, physiological stress resistance, and thus rate of cell aging. Impaired allostasis and impaired stress resistance seem inherent in most chronological aging. This raises the question of whether enhanced allostasis —the efficient response to stressors characteristic of youthful systems— is protective of biological aging and promotes longevity. More clinical studies are warranted to test whether decreases in psychological stress and increases in cellular stress resistance and neuroendocrine patterns of enhanced allostasis can indeed increase telomerase activity and telomere maintenance.

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