Molecular consequences of psychological stress in human aging

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Abstract

Psychological stress has often been described as a feeling of being overwhelmed by the necessity of constant adjustments to an individual’s changing environment. Stress affects people of all ages, but the lives of the elderly may particularly be affected. Major changes can cause anxiety leading to feelings of insecurity and/or loss of self-esteem and depression. The cellular mechanisms underlying psychological stress are poorly understood. This review focuses on the physical and molecular consequences of psychological stress linked to aging processes and, in particular, how molecular changes induced by psychological stress can compromise healthy aging.

Keywords:
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1. Introduction

By definition, psychological stress is an uncomfortable emotional experience accompanied by predictable biochemical, physiological and behavioral changes (Baum, 1990). To some extent, stress has beneficial effects; an activation of the sympathetic nervous system secreting the catecholamines adrenaline and noradrenaline, for example, is essential in the ‘fight or flight’ response. However this stress response also implicates immunosuppression, growth inhibition and enhanced catabolism and it is generally transient. Constant and persistent stress over an extended period of time does have health consequences.

1.1. Physical mechanisms involved in psychological stress

Three systems are directly involved in the physiology of stress: the nervous system, the endocrine system and the immune system, all of which can be affected by perceived threats (Everly, 2006). Two endocrine systems respond to psychological stress: the hypothalamic pituitary adrenocortical axis (HPA) and the sympathetic adrenal medullary (SAM) system. The primary effector of HPA activation in humans is cortisol, which is responsible for anti-inflammatory responses, metabolism of carbohydrates, lipids and proteins, and gluconeogenesis. Secretion of catecholamines occurs in response to SAM activation, which plays an important role in the regulation of cardiovascular, pulmonary, hepatic, skeletal muscle, and immune systems. Prolonged or repeated activation of the HPA and SAM systems can interfere with the control of other physiological systems, resulting in increased risk for physical and psychiatric disorders (Cohen et al., 1995; McEwen, 1998).

1.2. Psychological stress and diseases

Effects of stress on disease are supported by experimental evidence from animal as well as human studies. Exposure to chronic stress is known to result in long term or permanent changes in the emotional, physiological, and behavioral responses, which influence susceptibility to disease. High stress levels affect the immune, cardiovascular, neuroendocrine and central nervous systems (Anderson, 1998). People who suffer from depression and anxiety are at twice the risk for heart disease than people without these conditions (Anderson and Anderson, 2003). In addition, there is an association between acute and chronic stress and a person’s abuse of addictive substances (Sinha, 2008). Some studies have even suggested that unhealthy chronic stress management, such as overeating “comfort” food items, has contributed to the growing obesity epidemic (Dallman et al., 2003). Effects of stress on the regulation of immune and inflammatory processes have the potential to influence depression as well as infectious, autoimmune, and coronary artery disease and at least some types of cancer (Kiecolt Glaser et al., 2002). Psychological stress alters immune function through the release of HPA and SAM hormones that bind to and alter the functions of immune cells (Padgett and Glaser, 2003) and cortisol is able to cross the blood brain barrier and bind to receptors in the hippocampus. Long term production of stress hormones induces memory impairments, shrinking and atrophy of the hippocampus (Lupien et al., 1998). Psychological disorders are also associated with an increase in the production of reactive oxygen species (ROS) (Salim, 2014), and these may damage the DNA and increase cancer risk.

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1.3. Psychological stress and aging

Over time, the brain loses its capability of regulating hormone levels. Aging is associated with greater HPA axis reactivity to psychological stress (Trostadottir et al., 2005). Furthermore, in the elderly, stress may even increase the risk of Alzheimer's disease (Wilson et al., 2003). Stress comprises both an emotional and a physical component, and both can be especially detrimental in the elderly. In this context, it should be noted that chronic somatic illness, which is very common in the elderly, is also associated with increased rates of psychological disorders (Harter et al., 2007). Furthermore, elderly people can experience emotional and psychological stress not only related to increased disability and/or difficulty in carrying out daily activities but also related to increased health problems. Additionally, elderly people often experience a decreased sense of well-being and satisfaction with life, e.g., loneliness, isolation or loss of a loved one.

Successful aging involves the maintenance of mental, physical and social health and it is closely linked with quality of life. Butler (1991) defines it in terms of four dimensions of fitness: physical, intellectual, social, and purpose fitness (Butler, 1991). Physical fitness refers to muscle strength, resilience, and ability. Challenges, which often go hand in hand with aging and can cause both short term and chronic stress, may include serious illness, such as cancer, loss of memory, heart disease or arthritis.

1.4. Molecular consequences of psychological stress and aging

There is increasing evidence that psychological stress and mental disorders are associated with molecular and cellular signs of accelerated aging. However, the exact mechanisms by which stress influences aging processes are as yet unclear. Strikingly, a large body of data suggest that psychological stress may involve molecules believed to play a key role in cellular aging. It was demonstrated, for example, that women with the highest levels of perceived stress have telomeres shorter by the equivalent of at least ten years of additional aging compared to low stress women (Epel et al., 2004). Recently, several studies have added further weight to the association between traumatic stress and telomere length (Zhang et al., 2014; Jergovic et al., 2014; Shalev et al., 2014; Boks et al., 2014) suggesting that traumatic stress has an impact on aging at the cellular level. In perfect congruence with this finding are recent data on N-glycosylation profiling of plasma in patients suffering from post traumatic stress disorders (PTSD). Specific changes in the pattern of N-glycosylation had been shown to occur during aging and were proposed as a biomarker for physiological aging (Vanhooren et al., 2010). We could show recently that individuals with PTSD and trauma exposed individuals present a shift in the N-glycosylation profiles equivalent to an advancement of the aging process by 15 years (Moreno Villanueva et al., 2013) (Fig. 1).

Furthermore, accumulation of nuclear DNA damage has been discussed as a direct cause of aging (Best, 2009). Intriguingly, several studies also demonstrate significant correlations between psychological factors and DNA damage in humans (Gidron et al., 2006). We could show recently that patients suffering from PTSD as well as trauma exposed individuals show an accumulation of DNA damage, as detected by DNA single strand breaks in peripheral blood mononuclear cells (Morath et al., 2014) (Fig. 2).

Interestingly, recent work revealed a pathway involving β arrestin and the tumor suppressor protein p53, through which DNA damage may accumulate by chronic activation of the β-adrenergic receptor (Hara et al., 2011).

Aging is also associated with increased levels of circulating proinflammatory cytokines, a phenomenon known as "inflammaging" (Michaud et al., 2013). Mental health disorders have also been associated with elevated circulating proinflammatory biomarkers (Maes et al., 2012). Elevated levels of proinflammatory cytokines and chemokine abnormalities were detected in patients with panic disorder or PTSD.

Fig. 1. Scatterplot between the GlycoAge test and traumatic load (reprinted from Moreno-Villanueva et al., 2013, Transl Psychiatry, with permission). Low-stress controls, trauma-exposed and PTSD subjects are represented. Higher values in the GlycoAge test are positively correlated with traumatic load.

(Hoge et al., 2009), and more generally positive correlations between inflammation and trauma exposure have been reported (Tursich et al., 2014). It should be noted that in the short term, stress hormones inhibit the secretion of proinflammatory cytokines and promote the secretion of anti-inflammatory cytokines. A chronically activated HPA, however, leads to cortisol resistance, and prolonged chronic stress may increase proinflammatory cytokines while decreasing anti-inflammatory cytokines (Tian et al., 2014). Likewise, lymphocyte β2 adrenergic receptor density was negatively correlated not only with age but also with anxiety, depression, and anger hostility ratings (Yu et al., 1999). A recent publication shows evidence for the role of glucocorticoids in adrenocortical molecular mechanisms in response to psychological stress involved in aging and age related disorders (Hasan et al., 2012).

1.5. Effects of stress therapies on human physiology

Untreated chronic stress can result in serious health conditions including anxiety, insomnia, muscle pain, high blood pressure and a weakened immune system. Chronic stress can be treated with appropriate interventions such as lifestyle and behavioral change, psychotherapy, and in some situations, medication (McEwen, 2004). There are several kinds of psychiatric drugs such as antidepressants, anxiolytics, mood stabilizers and antipsychotics. The antidepressant effect of anti-psychotics involves the regulation of monoamines, glutamate, gamma-aminobutyric acid (GABA), cortisol, and neurotransmitter factors. However, they have adverse effects including extrapyramidal symptoms, weight gain, and hyperglycemia (Wang and Si, 2013). Fortunately, it has been shown that cognitive therapy can be as effective as medication (DeRubeis et al., 2005). But despite the extensive use of psychotherapy we still lack a biological perspective on how psychotherapy works. Changes in neurophysiology, such as heart rate, respiration rate, muscle tension, and galvanic skin resistance, electroencephalography and brain imaging markers have been detected after psychotherapy (Riess, 2011). Furthermore we have recently shown that accumulated DNA damage in peripheral blood mononuclear cells from PTSD patients disappeared after psychotherapy, providing proof of principle of the effect of psychotherapy on DNA integrity (Morath et al., 2014). Also physical exercise affects psychological well being (Norris et al., 1992). Physical activity plays a key role in the control of neuroendocrine, autonomic and behavioral responses to psychological stress. However, these responses might depend on the intensity of physical activity. Differential effects of the level of physical activity on different stress-related neurophysiological systems in response to psychosocial stress have been reported (Rimmele et al., 2009). Furthermore physical activity increases
the production of endorphins, a type of neurotransmitter in the brain, and helps in treating mild forms of depression and anxiety (Fox, 1999).

2. Discussion

Evidently there is a strong mutual relationship between physical health and psychological health. Due to the impact of psychological stress on human health there is a need for investigating the pathways involved in psychological stress at the cellular level. Psychological stress can be manifested in a number of biological markers, which may be useful for a better understanding of the underlying molecular mechanisms. Interestingly the same biomarkers identifying biological aging, e.g. telomere shortening, accumulated DNA damage, changes in N-glycosylation profiles, elevated levels of proinflammatory cytokines and deregulated stress hormone response are also found in several psychological disorders. This supports the idea that psychological stress may accelerate the somatic aging process, thus compromising healthy aging (Fig. 3). Hasan and collaborators propose that the excessive release of glucocorticoids is triggered by chronic psychological stress influencing the immune system, central nervous system, and endocrine system and concomitantly promotes aging (Hasan et al., 2012). In conclusion stress not only makes a person feel older, but in a very real sense, it can accelerate aging.

For older people, who are already at increased risk for illnesses, the managing of stress is particularly important. Older people are more likely to be offered medical therapies such as pharmaceuticals. But drug therapy can produce adverse effects and compliance problems. Other studies have found that social interactions can help older people stay mentally sharp and may reduce the risk of Alzheimer’s (Wilson et al., 2007). Moreover individuals with adequate social relationships have a 50% greater likelihood of survival compared to those with poor or insufficient social relationships (Holt-Lunstad et al., 2010).

Exercise can actually help block the effects of aging on cortisol levels. A recent study found that physically fit women in their mid 60s had essentially the same response to stress as a group of unfit women in their late 20s. In contrast, women in their mid 60s who were not physically fit released much larger amounts of cortisol in response to stress (Traustadottir et al., 2005). These findings suggest that appropriate exercise training may be an effective way of modifying some of the neuroendocrine changes associated with aging.

The importance of psychological treatment for patients with all kinds of somatic diseases is being increasingly recognized. However the molecular mechanisms involved in psychological stress responses are still poorly understood and there is a need for understanding the effects of psychotherapy on cellular processes. Learning to manage stress might give us a better chance to live a long and healthy life.

References


