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Chronic stress: a critical risk factor for atherosclerosis

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Abstract

Chronic stress refers to the non-specific systemic reaction that occurs when the body is stimulated by various internal and external negative factors over a long time. The physiological response to chronic stress exposure has long been recognized as a potent modulator in the occurrence of atherosclerosis. Furthermore, research has confirmed the correlation between atherosclerosis and cardiovascular events. Chronic stress is pervasive during negative life events and may lead to the formation of plaque. Several epidemiological studies have shown that chronic stress is an independent risk factor for the development of vascular disease and for increased morbidity and mortality in patients with pre-existing coronary artery disease. One possible mechanism for this process is that chronic stress causes endothelial injury, directly activating macrophages, promoting foam cell formation and generating the formation of atherosclerotic plaque. This mechanism involves numerous variables, including inflammation, signal pathways, lipid metabolism and endothelial function. The mechanism of chronic stress in atherosclerosis should be further investigated to provide a theoretical basis for efforts to eliminate the effect of chronic stress on the cardiocerebral vascular system.

Keywords

Atherosclerosis, cardiovascular disease, cerebrovascular disease, chronic stress, inflammation, lipid metabolism, inflammation

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Introduction

As cardiovascular and cerebrovascular diseases remain a major cause of death globally, it is necessary to identify all their risk factors to improve public health and reduce their societal burden. Atherosclerosis (AS) is a chronic disease that can develop at an early age; therefore, increasing attention is being paid to the contributions of adverse life circumstances that affect its risk and prevalence.[1] In psychology, chronic stress denotes a feeling of strain and pressure. Small amounts of stress may be desirable, beneficial and even healthy. However, excessive amounts of stress can be physically harmful. Research indicates that chronic psychological stress can increase the risk of atherosclerotic diseases, including strokes and heart attacks.[2]

Chronic stress is pervasive during negative life events and can lead to the formation of plaque in the arteries (AS). The relationship between stress and chronic disease is even stronger than that between stress and infectious or traumatic illness,[3,4] among both adults and adolescents.[5,6] Although physical activity is an important contributor to health, it does not significantly reduce the strong relationship between stress and accidental cardiovascular disease.[7] The effect of chronic stress on AS involves multiple complex mechanisms that remain to be fully elucidated.[8] Autonomic disorders caused by chronic stress may be a common mechanism that increases AS risk.[9] The resulting imbalances typically include one or more of the following aspects: inflammation, signal pathways, lipid metabolism, endothelial function and others. The secondary aspects include pathogen burden, heightened immunity, high-fat diet, depression, macrophage-specific reverse cholesterol transport (m-RCT), blood pressure, chromatin landscape and hematopoietic cells. Specifically, research shows that inflammation that may occur simultaneously with chronic stress is strongly related to endothelial dysfunction, an antecedent to AS and thrombotic disease.[10–12] Pain, heat, redness, swelling and loss of function are typical signs of inflammation, which is related to chronic stress.[13,14] Chronic stress may directly inhibit the diastolic function of a vessel via endothelial cells, and patients with long-term chronic psychological stress may develop diminished vascular endothelial function.[15] During the induction of chronic stress, the thoracic aortic ring shows high sensitivity to vasoconstrictors by inhibiting nitric oxide synthase activity or removing the endothelium.[16–20] Additionally, the signal is transmitted from the outside to the inner space of the cell along the signalling pathway to induce the cell to react. Many signal pathways may directly or indirectly contribute to the progress of AS under chronic stress. Lipids are substances that are vital for the supply and storage of energy, and are essential structural components of biofilms. One hypothesis is that the development of AS might be associated with dyslipidemia.[20,21] Furthermore, several experiments have demonstrated the vital function of stress-related hormones in the regulation of AS development by translating extra independent cholesterol from phagocytic macrophages and exporting it outside the cell.[22] Macrophages are important pluripotent cells that participate in the inflammatory response. Macrophage-derived foam cells contain high amounts of lipids and are central in the development of atherosclerotic plaque. Therefore, changes in the function of macrophages play a core role in the occurrence of AS.[23–25]

In this review, we aim to provide an overview of the role of chronic stress on the pathophysiological mechanism of AS.

Chronic stress effects on inflammation

Inflammation is a pathological process characterized by injury or destruction of

tissues caused by a variety of cytological and chemical reactions. The typical signs of inflammation are pain, heat, redness, swelling and loss of function, and inflammation is related to chronic stress.[13,14] Research shows that inflammation is strongly related to endothelial dysfunction, a preface to AS and thrombotic disease.[10–12] Inflammatory reactions are generally considered the main causes of AS, and the influence of mononuclear cells, different subtypes of lymphocytes, neutrophils and other immune and inflammatory cells on the pathological process of AS has been widely studied. However, in chronic stress, inflammation plays a critical role in the pathological process of AS. It is well-known that chronic stress can reduce hypothalamic–pituitary–adrenal axis activity and stimulate the sympathetic adrenal medulla, elevating production of inflammatory cytokines.[26–29] Symes et al. predicted that individuals with chronic stress would show greater changes in the serum levels of proinflammatory factors and cell adhesion molecules; they found that interventions had a moderate effect on vascular cell adhesion molecule-1 (VCAM-1).[30] VCAM-1, a member of the immunoglobulin gene superfamily, is mainly expressed in vascular endothelial cells, and its ligands are $\alpha4\beta1$ (VLA-4) and $\alpha4\beta7$. Its interaction with VLA-4 is involved in the inflammation induced by leukocytes and improves the pathological process of AS.[30,31]

Research indicates that the intercellular adhesion molecule-1, acute phase reactant C-reactive protein and proinflammatory cytokine interleukin-6 are significantly heightened in chronic stress-treated apolipoprotein E in knockout mice, compared with untreated animals.[2,32] Inflammatory signals have also been identified in plasma cluster of differentiation, interleukin-8, 5′-nucleotide ecto, programmed death ligand 1 and plasminogen activator inhibitor PAI-1.[33–35] Furthermore, chronic stress changes the homeostasis of the sympathetic and vagal nervous systems. Attenuation of the vagal tone contributes to a proinflammatory status, which can help to promote neurotransmitter regulation, particularly the spread of serotonin activation. For example, stress enhances the levels of plasma dipeptidyl peptidase-4 activity and weakens the concentration of plasma glucagon-like peptide-1 and both plasma and adipose adiponectin.[36–38]

However, further research is necessary to clarify whether the targeting of cyclic inflammatory factor or stress-related biomarkers may be an effective way to reduce the harmful effects of chronic stress.[39,40]

Chronic stress effects on lipid metabolism

Lipid metabolism is the physiological processes of biosynthesis (anabolism) and degradation (catabolism) of lipids. Diseases caused by abnormal fat metabolism are common in modern societies that experience chronic stress. Furthermore, there is experimental evidence that stress-induced hyperlipidaemia and increased oxidative stress are closely related to AS.[41–45]

Compared with control rats, rats exposed to chronic stress showed increases in the serum concentration of total cholesterol, triglycerides, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol and the atherogenic index, but no alteration in high-density lipoprotein cholesterol concentration.[46] To some extent, chronic social stress causes obesity through the excessive accumulation of fat, and research shows that obesity can increase the incidence of cerebrovascular diseases. Therefore, appropriate weight loss is beneficial for AS.[47,48] However, the accumulation of subcutaneous fat was associated with a remarkably low incidence of cardiovascular disease and a surprisingly

low mortality.[49] Previous research shows that chronic stress promotes visceral fat accumulation with subsequent generation of AS and cardiovascular events, rather than the accumulation of subcutaneous fat.[50]

Additionally, neuropeptide Y (NPY), a mediator between chronic stress and vascular lipid metabolism disorder, creates a stress-induced risk for lipid metabolic syndrome and AS. Understanding how NPY and its homologous receptors regulate lipid metabolism may generate meaningful data for future stroke therapies.[51,52]

Therefore, understanding the balance of lipid metabolism is essential for the study of chronic stress and AS.[53–56]

Chronic stress effects on hormones

A hormone is defined as a chemical substance that has a specific regulatory effect on the activity of a certain organ or organs. Chronic stress may affect quality of life;[57–60] however, the role of the stress-related adrenocorticotrophic hormone (ACTH) and cortisol in AS remains to be clarified. Some studies have posited that ACTH and cortisol affect the development of atherogenesis by regulating vascular endothelial action, including driving circulating monocytes to the vascular wall and causing them to disintegrate into macrophages, or by controlling the production of inflammatory interleukins.[22] Although corticosterone is an anti-inflammatory hormone, it can worsen AS in arteries, a process that is associated with increased dyslipidemia.[61] Moreover, one study showed that the amount of norepinephrine increased in a chronic stress experimental group.[62] Therefore, these hormones might be a novel target for the treatment and prevention of cardiovascular and cerebrovascular diseases.

Support for this suggestion comes from evidence that rosiglitazone is associated with the content of cyclic corticosterone; however, experimental data indicate that rosiglitazone does not prevent the occurrence of chronic cardiac angiopathy.[63] In addition, one study showed that the concentrations of cortisol and catecholamines were correlated with socioeconomic development levels, although there was no correlation with hormone levels and education and psychological factors.[64]Levels of cortisol and catecholamine increase as socioeconomic development levels rise and people's lives speed up.[64]

The sympathetic–adrenal–medullary system is another important factor in the pathogenesis of hypertension.[65] Under chronic stress, plasma epinephrine and norepinephrine are rapidly elevated. Previous studies indicate that the activity of the sympathetic nervous system is strengthened in hypertension; this sympathetic excitation can cause the small arteries and veins to contract, leading to an increase in the diastolic/systolic blood pressure.[66] Catecholamines are important hormonal messengers of the sympathetic–adrenal–medullary system and contribute to the shrinkage of peripheral vessels to increase diastolic blood pressure. The renin–angiotensin–aldosterone system also may play a critical role in chronic stress by increasing levels of angiotensin II, which regulates catecholamine secretion and blood pressure.[67–70] It is well-known that sympathetic nerve excitement can promote the secretion of renin by stimulating the juxtaglomerular cell and β receptors of local tissues, thus increasing angiotensin II production.

Regarding the role of hormones in the hypothalamic–pituitary–adrenal cortical axis,[71,72] chronic psychological stress stimulates the hypothalamus to secrete corticotrophin-releasing hormone and vasopressin, which can promote ACTH secretion. Glucocorticoid is essential to maintain the circulatory system's normal

response to catecholamines.[73] If glucocorticoid levels are low, the response obviously decreases, the myocardial contraction force weakens, the output drops and blood pressure decreases.[74–78] Some research suggests that there are racial and ethnic differences in the effects of chronic stress on blood pressure.[79]

Chronic stress effects on macrophages

Macrophages are relatively long-lived cells derived from blood monocytes. They may further differentiate within chronic inflammatory lesions into epithelioid cells or may fuse to form foreign body giant cells or Langhans giant cells. What role do macrophages play in the formation of atherosclerotic plaque under chronic stress? Studies have shown that the expression of cytokines produced mainly by stress-catecholamine macrophages increases under chronic mental stress.[23–25] Under stress, catecholamines bind to β adrenal receptors on the macrophage surface, inducing the expression of cytokines such as C-reactive protein, interleukin-1, interleukin-6 and tumour necrosis factor, which are all related to AS. In one study, individuals in the hypertensive group produced higher levels of macrophage superoxide anions than those in the control group; the findings suggest a potential mechanism underlying cerebrovascular risk for hypertension.[80]

In addition, a Type D (for "distressed") personality, a concept used in the field of medical psychology, may affect the progression of AS. Type D is defined as a combined tendency toward negative affectivity (e.g. worry, irritability, gloom) and social inhibition (e.g. reticence and a lack of self-assurance). Type D is a mental risk factor for poor cerebrovascular prognosis and increased death rate in individuals with atherosclerotic disease, but the mechanism is poorly understood. Macrophages play a vital role in the development of AS. Researchers tested the production of macrophage superoxide anions in individuals with cerebrovascular individuals with and without Type D. Type D participants showed a higher production of macrophage superoxide anions. This helps to explain the increased death rate in individuals with both cerebrovascular disease and Type D personalities.[81]

Other effects of chronic stress

Other factors associated with chronic stress include transport m-RCT, hematopoietic cells, pathogen burden, heightened immunity, high-fat diet and depression. Generally, after adjusting for covariance, a low education level is a significant independent predictor of pathogen burden. In one study, higher antibody responses were positively correlated with both low socioeconomic position and higher levels of chronic psychosocial stress, although the latter correlation was weaker.[82] The relationship between low socioeconomic status, chronic stress and increased AS morbidity may operate through a novel biological pathway of pathogen burden and heightened immunity.[82]

It is likely that there are sex differences in the effects of chronic stress.[83,84] Chronic stress syndrome, which is characterized by emotional instability, is likely to lead to increased morbidity from AS. One research study examined sex differences in endothelial cells and arterial elasticity, which are responsible for the progress of early atherosclerotic plaque. The outcomes demonstrated that AS morbidity in early life increased in men with higher levels of vital exhaustion and lower arterial elasticity, and indicated that women are better than men at coping with stressful mental atherosclerotic risk factors.[83]

A biological signalling pathway regulates the intracellular transfer of information (biological activation/inhibition). A study by Jin et al. showed that adjustment of the mitogen-activated protein kinase pathway increased the infarction area and decreased functional recovery in rat AS models of chronic stress.[85] Moreover, the progress of AS accelerates and the expression of toll-lie receptor 4 (TLR4)/nuclear factor-kappaB (NF-κB) is upregulated under chronic unpredictable mild stress (CUMS) in apolipoprotein E of knockout mice.[86] Therefore, the TLR4/NF-κB pathway may be involved in CUMS-induced AS through activation of inflammatory factors in these proteins.[86]

Physiological and biomorphic alterations of blood vessels induced by chronic stress may result in the progress of atherosclerotic plaque by a pathophysiological course associated with a shortage of nitric oxide production, leading to endothelial dysfunction.[20,87,88] Therefore, the maintenance of endothelial homeostasis is a new approach to prevent and treat AS.[89] Chronic stress also leads to autonomic nervous system imbalance and resulting overstimulation of the sympathetic nervous system. Diminished vagal tone promotes a proinflammatory state; subsequently, macrophages and microglia release proinflammatory cytokines and certain hormones, which can upregulate the rate-limiting enzymes in the tryptophan metabolic pathway.[10]

Lastly, Heidt and colleagues have reported the effects of chronic stress on hematopoietic stem cells in cardiovascular diseases.[90] Mariotti subsequently outlined how stress increases the concentration of cyclic inflammatory white blood cells, which are implicated in AS, by direct stimulation of hematopoietic stem cell proliferation.[91] Chronic stress stimulates the sympathetic fibres to release norepinephrine, which acts on mesenchymal stem cells located on the hematopoietic niche. The liver is central to reverse cholesterol transport (RCT), a beneficial process of lipid metabolism that removes excess cholesterol. There is evidence that a high-fat diet can reduce RCT-related gene expression; moreover, a combination of a high-fat diet and chronic unpredictable stress weakens the RCT process more seriously, which can aggravate AS.[92] m-RCT is another important antiatherogenic pathway that transfers cholesterol from macrophage foam cells to the liver and faeces. Long-term chronic stress is a pathogenic factor for AS.[93] Chronic stress likewise plays a very important role in the formation of hypertension, and its mechanism is now known to involve long-term activity of nerve and endocrine abnormalities, such as significantly increased levels of ACTH, cortisol, epinephrine, norepinephrine and angiotensin.[94] Long-term chronic stress activates the adrenal medullary system, promoting the division and differentiation of hematopoietic cells, and resulting in high coagulation and hypercoagulability that correlates with AS. There is a need for research on medications and biobehavioural therapeutic measures to reduce stress-hypercoagulability and the risk of thrombotic events.[95]

Conclusion

In summary, chronic stress is an independent risk factor for AS. Chronic stress causes stress hormones such as cortisol and catecholamines to regulate blood flow and blood pressure, leading to endothelial injury, platelet drilling and hematopoietic stem cell proliferation. The release of catecholamines as a result of sympathetic excitement not only causes coronary artery contraction, but also causes the rupture of vulnerable plaques. The increase of inflammatory cytokines and the expression of adhesion molecules via certain pathways can induce mononuclear cell aggregation

and lymphocyte adhesion. In addition, chronic stress leads to lipid metabolism imbalance, influences epigenetic patterns, induces depression, directly activates macrophages and promotes foam cell formation, inducing the formation of atherosclerotic plaque. The mechanism of chronic stress on AS should be further investigated to provide a theoretical basis for efforts to eliminate the effect of chronic stress on the cardiocerebral vascular system. In addition to positive control of risk factors, data shows that reducing chronic stress can effectively decrease stroke incidence.[96,97] For example, regular health examinations and stress prevention information are necessary for miners, long-term care workers and other individuals who experience chronic stress,[97,98] even though the concept of chronic stress is rarely applied in clinical work and daily life.[99]

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