Stress–Induced Atherosclerosis: Clinical Evidence and Possible Underlying Mechanism

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ABSTRACT

There is increasing recognition in medical fields of the importance of behavioral and psychosocial factors in the development of cardiovascular disease. Although the pathogenesis underlying stress-induced atherosclerosis is not well known, inflammation may play a key role. Activation of stress-induced neuroendocrine pathways, such as the hypothalamo-pituitary-adrenal axis, and the sympathetic nervous and renin angiotensin systems, direct neurogenic inflammation may also contribute to the development of stress-induced atherosclerosis. (Korean Circulation J 2005;35:101-105)

KEY WORDS: Stress; Atherosclerosis; Inflammation.

Introduction

Extensive studies support that behavioral and psychological factors contribute significantly to the development and prevention of atherosclerosis.1-4) Psychological factors, specifically depression, anxiety, personality factors, social isolation, and chronic and subacute life stress, are known to be related to the risk of coronary artery disease (CAD).21

Psychological Stress is Estimated as an Emerging Risk Factor for Atherosclerosis

Stress can be defined as a threat to homeostasis provoked by a variety of stressor, such as environmental, psychological or physiological factors.3) Chronic stress has been linked to the development of insulin resistance and deposition of abdominal fat, risk factors for CAD and diabetes in both humans and other primates.5) Social and psychological stress can provoke CAD in cynomolgus monkeys fed a low fat and low cholesterol diet, suggesting the possible role of stress in the development of atherosclerosis in people without traditional risk factors.4) Acute cardiovascular events and paradoxical arterial vasoconstriction are frequently triggered by physical or mental stress in susceptible patients.57) In a large prospective study, normotensive individuals, with high trait anger were at increased risk of combined CAD (acute myocardial infarction (MI) / fatal CAD, silent MI, or cardiac catheterization procedures) and hard events (acute MI / fatal CAD) compared with their lower anger counterparts.8) Similarly, the Framingham Heart Study demonstrated that suppressed anger independently predicted the 8-year incidence of CAD.9) Type A behavior pattern, a syndrome characterized by competition, hostility and exaggerated commitment to work, has received attention, because this personality trait is known to be associated with a 2-fold increased risk of CAD and 5-fold increased risk of recurrent MI over an 8.5 year follow up.10) Conversely, other studies have reported no correlation between type A behavior and CAD.11) Therefore, some other confounding factors, such as socioeconomic status, seem to be important variables for the risk of CAD. Interestingly, hostility, a major attribute of the type A pattern, has been estimated as a potential toxic element in this personality type. The results of studies to assess the relationship between hostility and CAD have been mixed, suggesting certain components of the hostility construct are more pathogenic.2) Work-related stress is the most widely studied chronic life stress related to CAD. Job strain, defined as jobs with high demand but low decision latitude, is associated with a 4-fold increase in the risk of cardiovascular death during a 6 year follow up,12) and when chronic, is positively associated with an increased risk of
cardiovascular disease. Mental stress-induced myocardial ischemia is known to be associated with a 2.8 fold higher rate of subsequent (mean 44 months follow up) fatal and nonfatal cardiac events, such as nonfatal MI, and coronary revascularization procedures. The role of stress in the progression of CAD has also been supported by the result of an intervention trial. Intensive lifestyle changes, including stress management, have been shown to significantly reduce angina attacks and adverse cardiac events, and reverse the degree of stenosis compared to a control group.

Physiological Pathways in Responding to Stress

Allostasis, defined as the ability to achieve stability through change, is critical to survival. Stress, as the allostatic load, can induce an allostatic response. The most common allostatic response involves the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis. Chemical mediators stimulated by stress activate the cells of paraventricular nucleus of hypothalamus (PVH) to produce corticotropin-releasing hormone (CRH), the key coordinator of stress. CRH activates the corticotrophs of the anterior pituitary gland to produce adrenocorticotropic hormone (ACTH), which stimulates the locus coeruleus to secrete norepinephrine (NE) at sympathetic nerve endings. Central activation of the SNS is transmitted to the adrenal medulla, where chromaffin cells are stimulated to produce epinephrine.

Stress can also activate the renin-angiotensin system (RAS), and central angiotensin receptors are important targets of stress regulation. Stress increases the production of circulating Ang II and the expression of its receptors in the brain, such as PVH. Stress-induced Ang II can activate the HPA axis through stimulation of hypothalamic CRH, and may contribute to the regulation of sympathetic responses to stress. Ang II has direct effects on the adrenal gland by stimulating aldosterone secretion from the zona glomerulosa and catecholamine release from the medulla. The effects of Ang II are mediated by two plasma membrane receptors, i.e. AT1 and AT2 subtypes. The majority of biological effects of Ang II occur following its binding to and activation of the AT1 receptor. There is crosstalk between AT1 and AT2 receptors, with stimulation of AT2 receptors opposing the effect of AT1 receptors. Stress was found to produce significant increases in the AT1 receptor numbers and mRNA in PVH, AT1B receptor mRNA and AT1 receptor binding in the zona glomerulosa of the adrenal gland and AT2 receptor mRNA in the locus coeruleus.

The effects of AT1 receptor antagonists on the stress-induced hormonal and sympatho-adrenal system elucidate the role of RAS in stress pathophysiology. Blockade of AT1 receptors by an intracerebroventricular injection of Losartan inhibited the stress-induced increases in plasma catecholamine and CRH mRNA in the PVH. Peripheral administration of Candesartan, an AT1 receptor antagonist, which can cross the blood brain barrier, reverses the stress-induced increases in AT1B mRNA in the adrenal gland zona glomerulosa, pituitary ACTH, and the secretions of adrenal corticosterone, aldosterone and catecholamine. These data suggest that endogenous Ang II induced by stress has a significant role in the activation of both the SNS and HPA axis.

Possible Mechanisms of Stress-Induced Atherosclerosis

Although much clinical evidence supports the concept of stress significantly contributing to CAD, the underlying mechanism is not well known. Enhanced activation of the SNS can induce inflammation of the vasculature, leading to atherosclerosis, and can increase platelet adhesion and aggregation, hemostasis, thrombosis, lipid mobilization and activation of macrophages. NE can control the release of CRH and enhance inflammation by stimulating the descending sympathetic signals. However, little is known of the biological pathways of neurogenic vascular inflammation. In addition to SNS activity, hypercortisolemia, resulting from the activation
Stress can induce inflammation in the peripheral organs via the neuro-endocrine system. It can be inferred that inflammation may act as a key mediator of stress-induced atherosclerosis. There are several inflammatory mediators contained within nerves that can be released by stress. These mediators include prostaglandin E2, neuropeptide Y (NPY), CRH, substance P (SP) and IL-6. NPY is a cotransmitter of sympathetic nervous innervation, which potentiates the action of NE, and can promote vascular smooth muscle cell proliferation, enhance leukocyte adhesion, platelet aggregation and macrophage activation. CRH may have a local direct effect on immune or inflammatory processes. Direct local administration of anti-CRH into the air pouch, simultaneously with carrageenin, an inducer of chemical inflammation, suppressed the inflammatory response to carrageenin, suggesting that CRH participates in the inflammatory process as a local stimulatory agent. Both somatic and autonomic nerves are associated with inflammatory cells, and nervous transmission induced by stress may result in neurogenic inflammation. Stress also increases the level of plasma proinflammatory cytokines, and may induce macrophage, having β-adrenergic receptors, to produce cytokines. One possible route to the stress-induced inflammation process is through the production of reactive oxygen species (ROS) subsequent to...
the activation of RAS. We found that arteries from rats subjected to stress showed endothelial dysfunction, as measured by the vascular tension in response to acetylcholine (Fig. 3). In our data, arteries of rats subjected to stress showed enhanced expression of endothelial adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1, decreased expression of endothelial nitric oxide synthase (e-NOS) mRNA and inactivation of nitric oxide (NO·), compared with the control group. Treatment of these rats with an ACE inhibitor significantly reversed both the stress-induced endothelial dysfunction and depression of e-NOS (unpublished data). Our data supports the hypothesis that “stress may inactivate NO·,” which is probably mediated by the activation of RAS; thereby inducing vascular inflammation and endothelial dysfunction.

Ang II, via activation of AT₁, has been implicated in cell migration, cell proliferation, coagulation, lipid oxidation and inflammation; thus, contributing to atherogenesis and endothelial dysfunction (Fig. 4). AT₁ receptor activation can lead to the production and release of ROS, such as superoxide (O₂·) and hydrogen peroxide (H₂O₂), in vascular cells, since AT₁ receptors are linked to the activation of NADH/NADPH oxidase in vascular cells. However, other pathways, such as xanthine oxidase, uncoupling of e-NOS, lipoxygenase/cyclooxygenase and Cyt P450 reductase, are known as sources of ROS production. When the production of ROS exceeds the ability for antioxidant defense, the resulting oxidant stress can evoke many pathophysiological conditions, such as diabetes and atherosclerosis. Oxidant stress can activate redox sensitive genes, such as VCAM, ICAM and monocyte chemoattractant protein-1 (MCP-1), thereby inducing inflammation and progression of atherosclerosis. Increased superoxide production in response to Ang II can inactivate NO· by forming peroxynitrite (ONOO⁻), which subsequently leads to endothelial dysfunction and promotion of atherosclerosis. Peroxynitrite is a powerful oxidant and cytotoxic agent that
can damage DNA, membrane lipids and mitochondria. Peroxynitrite promotes the inflammatory synthesis of prostaglandin 30 and is responsible for activating cyclooxygenase. The product of cyclooxygenase, PGH 2, is usually converted to PGI 2 by prostacyclin synthase. However, prostacyclin synthase is susceptible to attack by peroxynitrite; therefore, the accumulation of PGH 2 from cyclooxygenase can activate thromboxane receptors, resulting in vasoconstriction. This pathway may explain why susceptible patient complains of chest pain during stressful condition.

In conclusion, stress can induce atherosclerosis, which is probably mediated by inflammation. Various neuroendocrine pathways, such as the RAS and SNS, implicated in stress may participate in vascular inflammation. Future research to understand the mechanism of stress-induced atherosclerosis may elucidate the old curious association between mind and body.

REFERENCES