Review Article

Research on Psychoneuroimmunology: Does Stress Influence Immunity and Cause Coronary Artery Disease?

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Abstract

This review addresses the importance of psychoneuroimmunology (PNI) studies in understanding the role of acute and chronic psychological stressors on the immune system and development of coronary artery disease (CAD). Firstly, it illustrates how psychological stressors change endothelial function and lead to chemotaxis. Secondly, acute psychological stressors lead to leukocytosis, increased natural killer cell cytotoxicity and reduced proliferative response to mitogens while chronic psychological stressors may lead to adverse health effects. This will result in changes in cardiovascular function and development of CAD. Thirdly, acute and chronic psychological stressors will increase haemostatic factors and acute phase proteins, possibly leading to thrombus formation and myocardial infarction. The evidence for the effects of acute and chronic psychological stress on the onset and progression of CAD is consistent and convincing. This paper also highlights potential research areas and implications of early detection of immunological changes and cardiovascular risk in people under high psychological stress.

Key words: Cardiovascular, Inflammation, Psychoneuroimmunology, Stress

Introduction

In recent decades, there has been increasing interest in exploring the relationship between psychological stress and various health conditions. An enlarging body of evidence suggests the presence of interactions between the immune system, the central nervous system (CNS) and the endocrine system, where these systems can be influenced by psychological and social factors.1 In 1964, Solomon et al2 published an article entitled “Emotions, Immunity and Disease: A Speculative Theoretical Integration” and this probably became the beacon guiding research interest in psychoneuroimmunology (PNI). In 1975, Ader and Cohen et al3 demonstrated the possibility of immune function being classically conditioned and overhauled the belief then that immune system and nervous system did not interact. This spurred on the relentless effort to explore how behaviour and biological systems could interact in the endeavour to uncover more mysteries of the human body.

PNI is a field of investigation which examines relationships between stress, the immune system and health outcomes.4 Stress may reduce one’s coping ability and negatively impact neuroendocrine responses and ultimately, impair immune function. Traumatic events may dysregulate the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), leading to higher rates of serious and life-threatening illnesses including cardiovascular disease.5 Specifically, traumatic life events prime the inflammatory response system so that it reacts more rapidly to subsequent life stressors and the elevated inflammation has an aetiological role in many chronic diseases.5

Epidemiological studies indicate that psychosocial factors are strongly and independently associated with the development of coronary artery disease (CAD) and increase risk of cardiac dysfunction and cardiac events.6,7 It has been proposed that mental stress in everyday life is an important determinant of ambulatory ischaemia.8,9 Acute psychological stress is caused by short term emotional stress and intense anger.10 Chronic psychological stress is caused by low socioeconomic status, work stress, chronic strain, social isolation, depression, anxiety and hostility.10 In this paper, we review a selection of studies which addresses the role of psychological factors and progression of CAD and immune function. This allows clinicians to understand the importance of immunity as a link between the mind and the
cardiovascular system. This will also provide a foundation for building an integrative stress model to prevent CAD by preserving mental health.

**Stress Leading to Chemotaxis via Changes in Endothelium Function**

Psychological stress activates the SNS, which regulates heart rate and release of catecholamines, and the HPA axis, which regulates release of corticosteroids from the adrenal glands. In acute psychological stress, catecholamines predominantly affect natural killer (NK) cell circulation. The relationship between acute stress, SNS and leucocytes is illustrated in Figure 1. In chronic stress, the activity of the HPA axis may decrease, leading to fatigue and increased activation of immune-mediated inflammation.12-14

Furthermore, the stimulation of β-adrenergic receptors leads to an alteration of the expression of cell adhesion molecules (Fig. 2). Under low psychological stress, CD62L+ NK cells with L-Selectin adhesion molecules do not interact with endothelial cells. Under high psychological stress, increased concentration of adhesion molecules (ICAM-1, CD 11a) (Mills, 1996) leads to increased chemotaxis and monocyte and lymphocyte adhesion to endothelial cells via the sympathetic nervous system.

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**Fig. 1.** The relationship between acute stress, sympathetic nervous system and the white blood cells.

**Fig. 2.** Pathway showing how high stress levels lead to increased mononuclear cell adhesion to endothelial cells via the sympathetic nervous system.
natural killer (NK) cells with L-selectin (CD62 ligand) adhere loosely to the endothelial cells that express receptors of the adhesion molecule. Under high psychological stress, L-selectin from NK cells do not contribute to mobilisation and CD62+ NK cells will be retained in the vascular marginating pool or in the extravascular tissue.21 Instead, CD62- NK cells without L-selectin will be mobilised. Furthermore, there will be an increased concentration of adhesion molecules such as ICAM-1 and CD 11a under high psychological stress levels or loneliness. The increased concentration of adhesion molecules causes the CD62- NK cells to stop rolling and adhere to the site of increased adhesion molecules. Endothelial dysfunction also results in recruitment and adhesiveness of T lymphocytes and platelets.10 Activated T cells, in turn, produce proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1 and IL-6, which stimulate macrophages and vascular endothelial cells and amplify the downstream inflammatory process.10 This will eventually lead to an early state of atherosclerosis where macrophages and other immunocompetent cells cause local inflammation and formation of plaques.22 Local thrombus formation generates serotonin, thromboxane A₂ and thrombin, which cause vasoconstriction and subsequently lead to acute coronary syndromes (ACS) with rupture of the plaques. Acute phase protein such as the C-reactive protein (CRP) stimulates the smooth muscle and endothelial cells around coronary artery plaques, producing more proinflammatory cytokines and inducing expression of more adhesion molecules.10 CRP predicts an unfavourable course in ACS independent of the severity of atherosclerosis23 and is significantly associated with congestive heart failure (CHF).24

**Stress Leading to Coronary Artery Disease via Changes in Monocytes and Cytokines**

Figure 3 shows the roles of lymphocytes and cytokines in the development of CAD under acute stress and loneliness. Low socioeconomic status may increase the risk of CAD through moderating inflammation and immune activation.10 Low socioeconomic status is associated with
higher total T- and B-lymphocyte and NK cell counts in the circulation. Dopp et al.\textsuperscript{21} suggested that alternation in trafficking of specific lymphocyte subsets is an integral component of the fight-or-flight response to acute stressors. During acute psychological stress, the percentages of circulating NK cells and CD8\textsuperscript{+} cytotoxic T cells increase while those of circulating CD4\textsuperscript{+} T cells and NK cells that express L-selectin decrease.\textsuperscript{21,31} Acute psychological stress decreases proliferative responses to mitogens, particularly phytohaemaglutinin (PHA).\textsuperscript{14,29,32}

Owen and Steptoe\textsuperscript{29} studied the associations between NK cells, proinflammatory cytokine stress responsiveness and heart rate in humans. Increases in NK cell counts following stress were positively associated with heart rate responses and individual differences in sympathetically-driven cardiac stress responses were associated with NK and proinflammatory cytokine responses to psychological stress.

An acute psychological stressor increases proinflammatory cytokines including mononuclear cell IL-1\textbeta{} gene expression and plasma interleukin-6 (IL-6). The increased IL-1\textbeta{} gene expression was positively correlated with heart rate and systolic blood pressure reactivity.\textsuperscript{11} The cytokines also affect the brain and evoke feelings of malaise, sickness and tiredness.\textsuperscript{32-34} These cytokines can induce the proliferation and migration of smooth muscle cells by stimulating other growth factors that lead to coronary lesions.\textsuperscript{35} Mann\textsuperscript{36} suggested that the short-term expression of stress-activated cytokines within the heart may be an adaptive response to stress, whereas long-term expression of these molecules may be frankly maladaptive by producing cardiac decompensation. Cesari et al.\textsuperscript{24} found that proinflammatory cytokines predicted cardiovascular events in older persons. For example, IL-6 is significantly associated with CAD, stroke and congestive heart failure (CHF) and is a strong independent predictor for increased mortality in unstable CAD.\textsuperscript{24} Additionally, TNF-\alpha{} also shows a significant association with CAD. After all, the levels of cytokines such IL-6 and TNF-\alpha{} may be stronger predictors for incident cardiovascular events than those of acute phase protein such as CRP.\textsuperscript{24}

The Impact of Stress on Coagulation and Atherosclerosis

Figure 4 shows the relationship between stress and coagulation. Acute psychological stress increases haemostatic factors such as the von Willebrand factors.\textsuperscript{37} Adverse social circumstances and psychosocial factors in childhood increase the concentrations of acute phase proteins such as plasma fibrinogen in adulthood and this increases the subsequent risk of CAD.\textsuperscript{38} Lonely individuals also displayed greater fibrinogen response to stress.\textsuperscript{39} Chronic psychosocial stressors increase both haemostatic factors (e.g. Factor VII) and acute phase proteins (e.g. fibrinogen).\textsuperscript{37} Fibrinogen is thought to promote atherosclerosis by promoting platelet aggregation, enhancing release of endothelial-derived growth factors, stimulating smooth muscle cell proliferation and increasing plasma and whole blood viscosity.\textsuperscript{10} Acute and chronic stress may activate the coagulation cascade and lead to thrombus formation and myocardial infarction (MI). There is robust evidence from epidemiological studies and meta-analyses that higher levels of acute phase proteins such as CRP and fibrinogen predict future cardiovascular death and are associated with low socioeconomic status.\textsuperscript{10} Psychological stress is associated with increased platelet activation and increases the risk of cardiovascular disease.\textsuperscript{39}

Depression, Infection and Coronary Artery Disease

Depressive symptomatology such as fatigue and irritability are the precursors of first and recurrent CADs.\textsuperscript{40-47} Moreover, detailed investigations have shown that biological symptoms of depression such as malaise are modestly associated with lower left ventricular ejection fraction and the amount of vessel disease.\textsuperscript{46,47}

Previous research work indicated that Chlamydia
pneumoniae plays a role in atherosclerosis and is associated with a higher risk for CAD.48-53 In one study, depressive symptomatology is associated with a reactivation of latent viruses and inflammation of a coronary vessel.53 The difference between the depressed group and the control group with regard to the serum level of anti-Chlamydia pneumoniae IgG nearly reached significance. It requires further study to explore the effect of prolonged stress results in activation of Chlamydia pneumoniae, which may amplify the risk of CAD.

Future Directions

PNI facilitates the appreciation and understanding of stress responses. What do we know about the relationship between psychological stress and CAD? Research has demonstrated that acute psychological stressors lead to leukocytosis, increased CD8/CD4 ratios, increased NK cell cytotoxicity and reduced proliferative response to mitogen. These immunological changes will make individuals susceptible to CAD via increases in the expression of endothelial cell adhesion molecules and serum levels of acute phase proteins and haemostatic factors. It is now recognised that vascular inflammation is central to atherosclerosis, and that T lymphocytes, monocytes, and inflammatory cytokines are all involved.10 Chronic psychological stress may also lead to adverse health behaviours such as cigarette smoking, alcohol abuse, an unhealthy diet and reduced physical activity, which activate the above pathological mechanisms.

The above findings arouse curiosity in the possibility of enhancing immunity through coping with stress and reducing the psychosocial risk for cardiac conditions. Health psychology can be helpful in this identified relationship, as part of the importance of promoting health through psychological interventions. Health psychologists can help people cope with stress through interventions such as cognitive therapy, relaxation training and behavioural modifications.1 Research on stress and coping indicates that a variety of coping strategies (including relaxation, exercise, meditation and social support) used in response to stress enhances psychosocial functioning, physical health and quality of life.54-55 Improving global self-esteem is associated with lower heart rate and attenuated heart rate variations and inflammatory responses to acute stress.

Baseline CRP levels predict future cardiovascular events. CRP testing may have a major adjunctive role in the global assessment of cardiovascular risk.56 High-sensitive CRP monitoring may also offer a novel method of measuring response in antidepressant treatment.57 Measuring serum IL-1 and IL-6 levels may identify depressed or anxious patients who can benefit the most from a strategy of early prevention of cardiovascular disease.58

Studies in the past decade have addressed the relation of psychological stress to immune function and to CAD. Several questions remained unanswered: (i) To what extent do acute stressor effects found in the laboratory simulate more chronic real-life stressful events, and is laboratory immune reactivity a dispositional marker of susceptibility to stress-elicited disease?9-14 (ii) Exhaustion which occurs before an acute coronary event may form another part of the reaction to inflammation. Further research is required to find out whether the inflammation causes feelings of exhaustion or whether existing feelings of exhaustion are amplified by inflammation. (iii) Prospective studies of depressed patients are required to measure a wide array of inflammatory markers in order to identify those which are superior to the others in predicting CAD. Furthermore, the effects of established antidepressant therapies directed towards conventional cardiovascular risk factors on these biomarkers of inflammation should be further evaluated in outcome trials. Thereby it could be established if a reduction in these inflammatory markers corresponds to a reduction in cardiovascular events.

PNI is concerned with multifaceted psychosocial-neuroendocrine-immune system interactions. These include the influence of psychosocial factors such as stress perception and coping on immunologically mediated diseases. Chronic stress and associated psychological responses can activate the hypothalamic-pituitary-adrenocortical and sympathetic-adrenomedullary systems. Thus, further research can seek to investigate thoroughly the relationship between stress and immunity for cardiovascular conditions. The knowledge gained will be valuable, with the human health’s best interest at heart.

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