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Cardiovascular disease (CVD) is the leading cause of death in the developed world and a growing number of developing nations. In the United States, the estimated direct medical care costs for cardiovascular diseases totaled more than $240 billion in 2005, and these costs continue to escalate. CVD affects almost 35% of Americans aged 45-54, more than 50% of those aged 55-64, and more than 65% of those aged 65-74 years and is a leading cause of disability. Losses in productivity due to CVD are substantial, further contributing to the overall burden of CVD. The high social and economic cost of CVD, coupled with evidence demonstrating that the atherosclerotic process begins early in life, underscores the need for effective primary prevention efforts that address common modifiable risk factors for CVD. Among the most important of these are the physiological and anthropometric risk factors associated with insulin resistance syndrome (IRS) and the neuroendocrine and psychosocial alterations that may both predispose people to and result from these IRS-related abnormalities.

THE ROLE OF SYMPATHETIC AROUSAL, CHRONIC STRESS, AND RELATED FACTORS IN THE DEVELOPMENT OF INSULIN RESISTANCE SYNDROME AND CARDIOVASCULAR DISEASE

IRS, also referred to as syndrome X or metabolic syndrome, is a cluster of metabolic and hemodynamic abnormalities that together and independently predict the development of atherosclerosis and CVD. Core features of IRS are insulin resistance and associated hyperinsulinemia, glucose intolerance, atherogenic dyslipidemia (reduced high-density lipoprotein [HDL] and elevated triglycerides, free fatty acids, very low-density lipoprotein [VLDL], and small, dense LDL particles), high blood pressure, and abdominal obesity. Other abnormalities associated with IRS include impaired fibrinolysis and increased coagulability, chronic inflammation, endothelial dysfunction, and oxidative stress. Insulin resistance (ie, resistance to insulin-stimulated glucose uptake) is generally considered the primary underlying defect and a cardinal feature linking IRS with CVD.

Sympathetic hyperactivity, increased cardiovascular reactivity,
and reduced parasympathetic tone also have been strongly implicated in the pathogenesis of IRS and in the development and progression of CVD. 

Epidemiological studies have shown that enhanced cardiovascular reactivity to stress predicts the progression of atherosclerosis and increases risk for CVD morbidity and mortality. Similarly, studies in both humans and non-human primates strongly suggest that sympathetic hyperactivity can promote and exacerbate insulin resistance, hypertension, dyslipidemia, dysregulation of the HPA axis and sympathetic overactivity, and other components of IRS, promoting CVD, and related disorders. In addition, severe psychological stress may be due in part to excessive activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis. Human clinical studies have linked chronic life stress to enhanced sympathoadrenal reactivity and shown that psychological stress can increase arterial pressure; reduce HRV and baroreflex sensitivity; and trigger acute coronary events. Chronic stress also leads to the suppression of insulin-like growth factor-1 (IGF-1). As will be discussed in more detail later, reduced IGF-1 availability has been linked to the pathogenesis of glucose intolerance, hypertension, atherosclerosis, CVD, and related disorders.

Likewise, prospective epidemiological studies indicate that chronic psychosocial stress can lead to the development of hypertension and other features of IRS promote CVD, and lead to an increase in CVD mortality.

Studies in both human populations and primate models have linked psychological stress to the development and exacerbation of negative emotional states, including depression, anxiety, hopelessness, hostility, and anger. Characterized by dysregulation of the HPA axis and sympathetic overactivity, such negative affective states are, in turn, associated with increased risk for visceral obesity, hypertension, insulin resistance, dyslipidemia, and other components of IRS, as well as for stroke, diabetes, and CVD morbidity and mortality. Mechanisms underlying the link between psychosocial stress and negative affective states may include stress-related elevations in proinflammatory cytokines, which have been prospectively related to symptoms of depression, anxiety, and associated cognitive impairment and recently associated with anger, hostility, and aggression in both humans and animal models.

In short, psychosocial factors can have a profound impact on the development and progression of CVD. The mechanisms linking chronic stress to the development of atherosclerosis, CVD, and related outcomes are not yet completely understood. However, dysregulation of the HPA axis and sympathoadrenal system is thought to play a central role. The putative pathological sequelae of chronic stress are summarized in the Figure and reviewed in detail below.

**THE STRESS RESPONSE AND THE PATHOLOGICAL SEQUELAE OF CHRONIC STRESS**

**Neurobiology of Stress**

Stress can be defined as exposure to perceived or actual hostile conditions (stressors) and can include any psychological, environmental, or physiological threat to well-being or homeostasis. Exposure to real or perceived danger triggers a programmed, integrated, multi-system response that, under conditions of genuine danger, enhances the probability of survival. Disturbing experiences and other sources of stress activate the HPA axis and sympathoadrenal system, triggering a cascade of autonomic, immune, and behavioral responses collectively

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**Figures and Diagrams**

- **Diagram 1:** Pathological Sequelae of Chronic Stress
  - **Adverse Cardiovascular Responses:**
    - Heart rate, HRV, baroreflex sensitivity, endothelial function, oxidative stress, coagulopathy
  - **HPA Axis Activation:**
    - Insulin resistance, glucose intolerance, dyslipidemia, visceral adiposity, hypertension
  - **SNS Activation:**
    - Norepinephrine, epinephrine, cortisol
  - **Structural Remodeling of Hippocampus and Amygdala**
  - **Systemic Inflammation**

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**Table 1:** Key Features of IRS

- Insulin resistance, glucose intolerance, dyslipidemia, visceral adiposity, hypertension

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**Table 2:** Cardiovascular Disease Outcomes

- Stroke, diabetes, and CVD morbidity and mortality

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**References**

1. Stress and Insulin Resistance-related Indices of Cardiovascular Disease

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**Note:** The full text includes detailed discussions and references that are not fully transcribed due to the text's complexity and the need for explicit referencing of specific studies and mechanisms.
termed the stress response. Pupils are dilated, attention is sharpened and focused on the perceived threat, defensive behaviors are initiated, cardiovascular output and respiration accelerate, catabolism increases, and blood flow is redirected to provide maximal perfusion and fuel to the brain, heart, and muscles. Gut motility is reduced, feeding and appetite are suppressed, and growth and reproductive function are inhibited.55,63,103

The stress response is regulated primarily via the HPA axis and the sympathoadrenal system.101 The classic neuroendocrine cascade is initiated by the central secretion of catecholamine, norepinephrine, and other chemical mediators, which stimulate release of corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) by the CRF-AVP-secreting neurons of the paraventricular nucleus of the hypothalamus into the hypophyseal portal system. CRF, the primary coordinator of the stress portal system, induces the brainstem locus ceruleus to secrete norepinephrine at sympathetic nerve endings.55,102 Impulses transmitted by sympathetic fibers in the splanchnic nerve stimulate the adrenal medulla to produce epinephrine; epinephrine further potentiates HPA axis and sympathetic nervous system activity. Within seconds, CRF also induces the secretion of pituitary adrenocorticotropic hormone (ACTH); in turn, ACTH stimulates the adrenal cortex to produce glucocorticoids, the final effectors of the HPA axis.55,63,100,103 Blood cortisol levels begin to rise several minutes later, peaking between 30 and 60 minutes after the onset of the stressor.102 Stress-induced secretion of CRF and cortisol inhibits pituitary gonadotropin and growth hormone secretion and renders the target tissues of sex steroids and growth factors resistant to these substances.5,51 Sympathetic innervation to the kidney may also lead to the production of renin and ultimately angiotensin II, a potent vasoconstrictor that raises blood pressure and heart rate.59 Stress-induced catecholamines also can stimulate the production of proinflammatory cytokines.55,58,59 The release of inflammatory cytokines can further augment and prolong the stress response by exerting a powerful stimulating effect on the HPA axis55,106,107 and inducing (lymphocyte) resistance to the negative feedback effects of glucocorticoids.43

The brain’s limbic system—in particular, the hippocampus and amygdala—also plays a key role in the stress response.12,13,58,108 These structures are targets for stress hormones108,109 and are integrally involved in stress-related learning and memory processes and in the formation of conditioned behavioral and emotional responses.98,101,111 The amygdala is considered the main neural locus for fear-related conditioning and behaviors,61,112 facilitating the association of environmental cues and events with negative emotions and tailoring behavioral and emotional responses to past experiences. The hippocampus plays a central role in learning and memory,69 the perception and processing of pain,98,112 and the regulation of certain autonomic functions, including ACTH release.48 Stress levels of glucocorticoids act on the central nucleus of the amygdala to increase the activity of CRF-AVP-secreting neurons, thereby amplifying the response of the CRF system and glucocorticoid secretion during stress.103 Stress-induced catecholamine release not only activates the HPA axis, but acts on the amygdala, hippocampus, and related structures to enhance long-term storage of aversive emotional memories10,112 and to generate and consolidate associated conditioned responses.113

**Pathological Effects of Chronic Stress**

Although the stress response can enhance the probability of survival in the face of true environmental threats, repeated activation in response to frequent or chronic stress can have serious pathological sequelae. Recurrent or chronic evocation of the HPA axis leads to excessive and prolonged cortisol and catecholamine secretion,55,56,114 which can initiate a destructive physiologic cascade. Cortisol has direct as well as insulin-mediated effects on adipose tissue, ultimately promoting insulin resistance, visceral adiposity, dyslipidemia, relative glucose intolerance, and hypertension, core features of IRS.55,63,100,114 For example, prolonged and excessive secretion of cortisol promotes insulin resistance and accumulation of triglycerides in adipocytes and increases lipoprotein lipase activity, leading to the release of free fatty acids and consequent hyperinsulinemia.108 Glucocorticoids both directly and indirectly impair insulin action and also may increase hepatic glucose metabolism and inhibit glycolgen synthesis, further contributing to impaired glucose metabolism.90,114 Cortisol inhibits pituitary responsiveness to gonadotropin-releasing hormone, suppresses secretion of growth hormone and thyroid-stimulating hormone, and renders the target tissues of sex steroids and growth factors resistant to these substances.60 High levels of cortisol and insulin, coupled with low levels of growth hormone and sex steroids, may lead to lipid accumulation, especially in the visceral area.59

Elevated catecholamines, together with increased renin and angiotensin II, contribute directly to elevated blood pressure, increased heart rate, deleterious structural and functional alterations in the vascular wall,115,116 platelet hyperactivity, and activation of the coagulation cascade.55,58,118-121 In addition, increased catecholamine levels directly and indirectly reduce insulin sensitivity122-124 and promote related downstream changes consistent with IRS.124-127 In turn, insulin resistance and compensatory hyperinsulinemia, as well as visceral adiposity, impaired glucose metabolism, and other components of IRS promote HPA axis activation and enhance sympathetic tone,123,125,126 further contributing to a pathologic and self-perpetuating cycle of events.

Chronic psychosocial stress also has been linked to increased oxidative stress,59 endothelial dysfunction,55,60 and procoagulation changes.55,56 These alterations are thought to reflect, in part, downstream effects of IRS.126,128 Hyperglycemia, visceral adiposity, and elevations in triglycerides and free fatty acids lower antioxidant defenses and increase production of free radicals.120 Free radicals cause oxidative imbalance within tissues. Oxidative imbalance exacerbates insulin resistance129 and may mediate many of the atherosclerotic and thrombotic changes that are associated with IRS124-125 and the development of CVD.19 Increased visceral adiposity, insulin resistance, hyperglycemia, dyslipidemia, and associated increases in oxidative
Stress and Insulin Resistance-related Indices of Cardiovascular Disease

Chronic Stress and Reduced Insulin-like Growth Factor-1

Chronic or recurrent stress also leads to the suppression of IGF-1 via CRF-induced elevations in cortisol and inhibition of growth hormone. If IGF-1, a small polypeptide that is structurally related to insulin, is an essential surviving factor for cell proliferation and differentiation. IGF-1 also plays an important role in glucose and energy metabolism; acts as an antioxidant in the heart and other organs, including the brain; inhibits inflammation by antagonizing TNF-α; and has well-documented neuroprotective effects, which are detailed below. Reduced IGF-1 bioavailability is thought to aid in the promotion of atherosclerosis due to resulting impairment in the growth, repair, and survival of vascular smooth muscle cells. Reduced IGF-1 bioavailability of IGF-1 also may contribute to CVD by altering carbohydrate and lipid metabolism, and experimental studies in tree shrews and marmosets have shown that these structural changes are accompanied by progressive declines in both memory and cognitive function, and, in animal models, by increased fear conditioning, anxiety, and aggressive behavior. In addition, there is mounting evidence that the beneficial effects of chronic antidepressants on mood and cognition may be mediated largely by the stimulation of neurogenesis in the hippocampus, suggesting that depressed neurogenesis and related changes may be an important causal factor in the etiology of depression.

The adverse effects of chronic stress on neural structure and function are likely mediated by persistent elevation in corticosteroids, the down-regulation of IGF-1, and the ensuing production of free radicals and impairment of glucose metabolism. Due to its high metabolic rate, the hippocampus is very sensitive to local tissue concentrations of glucose. Impairment in glucose metabolism can thus have serious adverse effects on hippocampal structure and function, perhaps helping to account for the reduced hippocampal volume associated with diabetes and depression. Cortisol infusion produces a rise in blood glucose and inhibits glucose uptake in the hippocampus; chronic glucocorticoid treatment produces remodeling of the hippocampus mirroring that induced by chronic stress. In addition, rising cortisol levels over 5 years have been shown to predict hippocampal atrophy in humans. Elevated glucocorticoids may inhibit neurogenesis and promote dendritic remodeling in part via the down-regulation of IGF-1. IGF-1 has several neuroprotective effects, including the promotion of neurogenesis, neuronal development and differentiation, synapse formation, and glucose utilization throughout the brain. Experimental studies have shown IGF-1 administration to attenuate the reduction in neurogenesis and cognitive function with stress and aging, enhance glucose uptake in the aging hippocampus, and protect against neuronal apoptosis associated with chronic stress. Circulating IGF-1 also stimulates neurogenesis in the dentate gyrus of the hippocampus. In contrast, experimental reduction of IGF-1 via immunoneutralization blocks the promotinal effects of exercise on hippocampal cell division.

The damaging effects of chronic stress on neural structure...
and function contribute further to HPA axis dysregulation, sympathetic reactivity, and the development of adverse mood states, which in turn promote atherogenic changes and, ultimately, the development of CVD and other chronic insulin-resistance conditions. Although these stress-induced changes in the brain can have serious and potentially devastating effects, they are reversible, at least in the earlier phases. These findings highlight the importance of timely therapeutic intervention. Given the importance of psychosocial factors and sympathetic activation in the development and progression of IRS and CVD, yoga and other mind-body therapies may be effective strategies for reducing CVD risk.

CONCLUSION

Chronic psychosocial stress can lead to a destructive, self-perpetuating cascade of physiologic and structural changes that promote the development of IRS, atherosclerosis, and ultimately CVD. Research suggests that adverse psychosocial factors and associated dysregulation of the sympathoadrenal system and HPA axis play a central role in the pathogenesis of these disorders; hence, certain mind-body modalities may offer particular promise in the prevention and management of CVD and related insulin-resistant states.

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