CHRONIC STRESS AND INSULIN RESISTANCE– RELATED INDICES OF CARDIOVASCULAR DISEASE RISK, PART I: NEUROPHYSIOLOGICAL RESPONSES AND PATHOLOGICAL SEQUELAE

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Cardiovascular disease (CVD) is the leading cause of death and disability in the industrialized world, and the prevalence is increasing rapidly among developing nations. The rising prevalence of CVD worldwide may be attributed in large part to specific atherogenic changes in insulin resistance, adiposity, lipid profiles, and other indices of insulin resistance syndrome (IRS), a cluster of metabolic and hemodynamic abnormalities that are strongly predictive of CVD. A growing body of research suggests that chronic psychosocial stress and related factors significantly contribute to the pathogenesis of IRS-related abnormalities, associated insulin-resistant states, and CVD, in part by promoting dysregulation of the sympathoadrenal system and hypothalamic-pituitary-adrenal axis. In this article, we review the literature supporting the relationships between these factors, outline the neurophysiologic responses to chronic stress, and discuss the pathways by which chronic or recurrent psychosocial stress may lead to a destructive cascade of neuroendocrine, metabolic, inflammatory, and neuropsychological changes that fosters the development of IRS and, ultimately, CVD. (*Altern Ther Health Med.* 2007;13(4):46-52.)

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Cardiovascular disease (CVD) is the leading cause of death in the developed world[1-4] and a growing number of developing nations.[5-8] In the United States, the estimated direct medical care costs for cardiovascular diseases totaled more than $240 billion in 2005,[1] 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.[1] Losses in productivity due to CVD are substantial, further contributing to the overall burden of CVD.[1,9] The high social and economic cost of CVD, coupled with evidence demonstrating that the atherosclerotic process begins early in life,[10] 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.[4,11-14] 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.[11,13-15] Other abnormalities associated with IRS include impaired fibrinolysis and increased coagulability,[13,16-18] chronic inflammation,[13-15,18] endothelial dysfunction,[13,19,20] and oxidative stress.[19] Insulin resistance (ie, resistance to insulin-stimulated glucose uptake) is generally considered the primary underlying defect and a cardinal feature linking IRS with CVD.[18,19,21-23]

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.[24-30] Epidemiological studies have shown that enhanced cardiovascular reactivity to stress predicts the progression of atherosclerosis and increases risk for CVD morbidity and mortality.[31,32] Similarly, studies in both humans and non-human primates strongly suggest that sympathetic hyperactivity can promote and exacerbate insulin resistance,[24,33] hypertension,[24,33,34] dyslipidemia,[33] visceral obesity,[33] and other components of IRS,[25,35] accelerate the development of atherosclerosis,[25,35] and ultimately contribute to the development and progression of cardiovascular disease.[24,25,34-36] Reductions in cardiovagal function also have been associated with IRS.[13,37,38] Insulin resistance, elevated lipids, obesity, and other components of IRS also can lead to a reduction in heart rate variability (HRV)[26,39,40] and baroreflex sensitivity,[37,38,41] factors thought to reflect impaired cardiovagal adaptability and reduced parasympathetic tone.[42-44] Reductions in HRV and baroreflex sensitivity are, in turn, strong independent predictors of cardiovascular morbidity and mortality[26,37,39,45] and may in part mediate the effect of IRS-related abnormalities on these outcomes.[37,39,41]

Recent experimental, clinical, and epidemiological studies offer compelling evidence that chronic stress and related psychosocial factors contribute significantly to the pathogenesis and progression of IRS and CVD.[25,27,28,46-49] Studies using primate models have demonstrated that chronic psychosocial stress induces hypercortisolemia,[25,28,50] insulin resistance, and visceral adiposity;[51] accelerates atherosclerosis; and exacerbates endothelial dysfunction.[25,51] These effects are strongly associated with the subsequent development of CVD and are thought to be due in part to excessive activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis.[25,35,52] Human clinical studies have linked chronic life stress to enhanced sympathoadrenal reactivity[53] and shown that psychological stress can increase arterial pressure; reduce HRV;[54] induce proinflammatory[55] and procoagulation changes;[25,55,56] raise fasting levels of glucose, insulin, and lipids;[57] increase oxidative stress;[58] impair endothelial function;[59-61] and trigger acute coronary events.[25,62] Chronic stress also leads to the suppression of insulin-like growth factor-1 (IGF-1).[63] 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.[64-71] Likewise, prospective epidemiological studies indicate that chronic psychosocial stress can lead to the development of hypertension[49,72] and other features of IRS,[57,73] promote CVD,[27,48,55,62,72,74] and lead to an increase in CVD mortality.

Studies in both human populations and primate models also have linked psychological stress to the development and exacerbation of negative emotional states, including depression, anxiety, hopelessness, hostility, and anger.[25,28,50,55] Characterized by dysregulation of the HPA axis and sympathetic overactivity,[42,55,75] such negative affective states are, in turn, associated with increased risk for visceral obesity,[76,77] hypertension,[49,78,79] insulin resistance,[80-82] dyslipidemia,[82,83] and other components of IRS,[42,82,84]
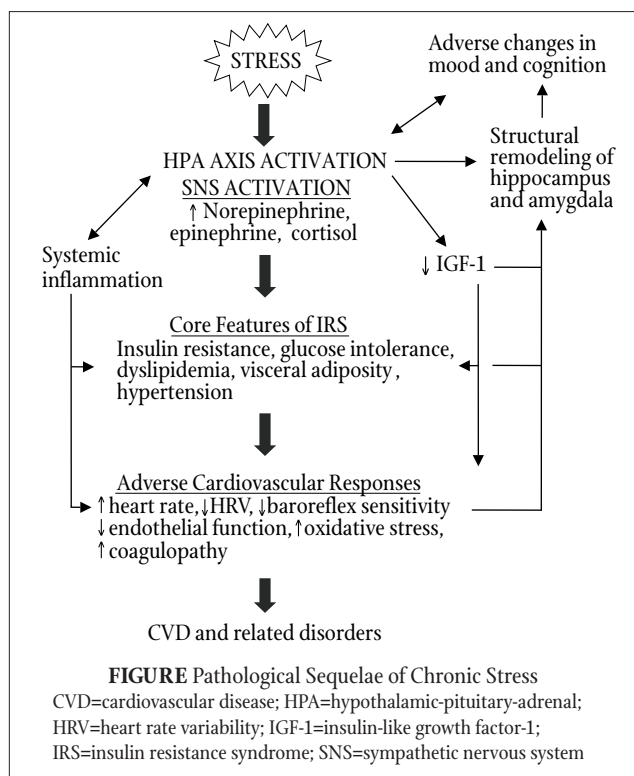
as well as for stroke,[85] diabetes,[86-88] and CVD morbidity[27,42,47,62,72,79,89] and mortality.[42,47,90] Mechanisms underlying the link between psychosocial stress and negative affective states may include stress-related elevations in proinflammatory cytokines, which have been prospectively related to symptoms of depression, anxiety, and associated cognitive impairment[91-95] and recently associated with anger, hostility, and aggression in both humans and animal models.[96,97]

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.[52,98-101] 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.[102] Disturbing experiences and other sources of stress activate the HPA axis and sympathoadrenal system, triggering a cascade of autonomic, immune, and behavioral responses collectively

FIGURE Pathological Sequelae of Chronic Stress
CVD=cardiovascular disease; HPA=hypothalamic-pituitary-adrenal; HRV=heart rate variability; IGF-1=insulin-like growth factor-1; IRS=insulin resistance syndrome; SNS=sympathetic nervous system

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.[55,63,102]

The stress response is regulated primarily via the HPA axis and the sympathoadrenal system.[103] 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 response, 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 adrenocorticotropin (ACTH); in turn, ACTH stimulates the adrenal cortex to produce glucocorticoids, the final effectors of the HPA axis.[55,63,102,103] 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.[51,63] 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.[55] Stress-induced catecholamines also can stimulate the production of proinflammatory cytokines.[55,104,105] The release of inflammatory cytokines can further augment and prolong the stress response by exerting a powerful stimulating effect on the HPA axis[55,106,107] and inducing (lymphocyte) resistance to the negative feedback effects of glucocorticoids.[93]

The brain's limbic system—in particular, the hippocampus and amygdala—also plays a key role in the stress response.[63,99,108,109] These structures are targets for stress hormones[109,110] and are integrally involved in stress-related learning and memory processes and in the formation of conditioned behavioral and emotional responses.[108,110,111] The amygdala is considered the main neural locus for fear-related conditioning and behaviors,[63,111] 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,[109] the perception and processing of pain,[108,112] and the regulation of certain autonomic functions, including ACTH release.[109] 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.[113] 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 memories[63,110] and to generate and consolidate associated conditioned responses.[110]

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,[63,100,114] 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.[23,63,101,114] 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.[114] Glucocorticoids both directly and indirectly impair insulin action and also may increase hepatic glucose metabolism and inhibit glycogen synthase, further contributing to impaired glucose metabolism.[101,114] 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.[63] 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.[50]

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,[115-117] platelet hyperactivity, and activation of the coagulation cascade.[55,56,118-121] In addition, increased catecholamine levels directly and indirectly reduce insulin sensitivity[122-124] 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,[24,63,126-129] further contributing to a pathologic and self-perpetuating cycle of events.

Chronic psychosocial stress also has been linked to increased oxidative stress,[58] endothelial dysfunction,[59-61] and procoagulation changes.[55,56] These alterations are thought to reflect, in part, downstream effects of IRS.[19,126] Hyperglycemia, visceral adiposity, and elevations in triglycerides and free fatty acids lower antioxidant defenses and increase production of free radicals.[130-133] Free radicals cause oxidative imbalance within tissues. Oxidative imbalance exacerbates insulin resistance[133] and may mediate many of the atherosclerotic and thrombotic changes that are associated with IRS[134,135] and the development of CVD.[134] Increased visceral adiposity, insulin resistance, hyperglycemia, dyslipidemia, and associated increases in oxidative

stress[60,61,136] combined with shear stress due to elevated blood pressure[56] impair endothelial function,[137] lead to vascular injury,[138] and promote platelet hyperactivity, activation of the coagulation cascade, and hypofibrinolysis.[119,139] Given that the endothelium regulates vascular tone, coagulation, thrombus formation, and proliferative growth,[19,23,136,140] it is critical to maintain optimal endothelial function. Damage to the endothelium and associated coagulopathic changes can both induce and be exacerbated by inflammation[55,126] and insulin resistance,[19,23,141] increase blood pressure and cardiovascular reactivity, and promote artiolar narrowing, plaque formation, and vascular permeability,[23,117,136] ultimately leading to the development of CVD.[23,126,136,142]

Chronic Stress and Inflammatory Cytokines

Prolonged sympathoadrenal activation,[55] together with elevated free fatty acids[143] and other components of IRS,[55,126] increases production of proinflammatory cytokines, leading to chronic inflammation of the vascular wall.[55] There is growing evidence that these inflammatory cytokines promote oxidative stress[105,144] and endothelial dysfunction,[145] exacerbate insulin resistance and related abnormalities,[21,146] and ultimately foster the development and progression of atherosclerosis, acute coronary syndromes,[21,104,145,147,148] diabetes,[21,104,146] and related disorders.[104] Proinflammatory cytokines also activate the HPA axis and sympathoadrenal system[24,55,149] and may contribute to the onset of depression and other negative affective states,[91,93-95,149-150] thereby further exacerbating the pathological effects of chronic stress.

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.[63] IGF-1, a small polypeptide that is structurally related to insulin, is an essential surviving factor for cell proliferation and differentiation.[64] IGF-1 also plays an important role in glucose and energy metabolism;[64,66,67] acts as an antioxidant in the heart and other organ systems, including the brain;[64] inhibits inflammation by antagonizing TNF-α;[151] and has well-documented neuroprotective effects, which are detailed below.[109,151-153] 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.[154,155] Reduced bioavailability of IGF-1 also may contribute to CVD by altering carbohydrate and lipid metabolism.[65,67,156,157] Recent clinical and experimental studies indicate that reduced IGF-1 levels contribute to impaired glucose metabolism, insulin resistance, dyslipidemia, central adiposity, and hypertension,[64-68] and low levels of IGF-1 have been associated with the development of both diabetes and CVD.[64,69-71] For example, in a large prospective study of Danish adults who were free of ischemic heart disease (IHD) at baseline, low IGF-1 levels were strongly and independently associated with increased risk of IHD later in life,[69] supporting a role for IGF-1 in the pathogenesis of cardiovascular disorders.

Chronic Stress and Brain Remodeling

Chronic stress can lead to the remodeling and atrophy of the hippocampus and other brain structures.[99,103,105,108,109] For example, repeated stress in rats reduces dendritic branching and cell survival and suppresses neurogenesis in the hippocampal dentate gyrus,[110] one of the few areas of the mammalian brain that continues to generate neurons into adulthood.[158] Similarly, recent experimental studies in tree shrews and marmosets have shown psychosocial stress to inhibit cell proliferation[159-161] and impair cell survival in the dentate gyrus[160] and to decrease dendritic branching of CA3 pyramidal neurons.[159,160] Major depression can likewise lead to progressive atrophy of the hippocampus,[110,149] along with other brain structures involved in the stress response, including the amygdala and prefrontal cortex.[108-110] Both clinical and experimental studies have shown that these structural changes are accompanied by progressive declines in both memory and cognitive function,[99,109,110] and, in animal models, by increased fear conditioning, anxiety, and aggressive behavior.[110] In addition, there is mounting evidence that the beneficial effects of chronic antidepressants on both mood and cognition may be mediated largely by the stimulation of neurogenesis in the hippocampus,[159,162-165] suggesting that depressed neurogenesis and related changes may be an important causal factor in the etiology of depression.[164]

The adverse effects of chronic stress on neural structure and function are likely mediated by persistent elevation in corticosteroids,[99,105,108,109] the down-regulation of IGF-1,[153] and the ensuing production of free radicals and impairment of glucose metabolism.[105,108,109,166] Due to its high metabolic rate, the hippocampus is very sensitive to local tissue concentrations of glucose.[109] 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[109] and depression.[109,166] 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.[109,110] In addition, rising cortisol levels over 5 years have been shown to predict hippocampal atrophy in humans.[108]

Elevated glucocorticoids may inhibit neurogenesis and promote dendritic remodeling in part via the down-regulation of IGF-1.[153] IGF-1 has several neuroprotective effects, including the promotion of neurogenesis, neuronal development and differentiation, synapse formation, and glucose utilization throughout the brain.[109,151-153] 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[109-153] associated with chronic stress. Circulating IGF-1 also stimulates neurogenesis in the dentate gyrus of the hippocampus.[153] In contrast, experimental reduction of IGF-1 via immunoneutralization blocks the promotional effects of exercise on hippocampal cell division.[109,153]

The damaging effects of chronic stress on neural structure

and function contribute further to HPA axis dysregulation,[63] sympathetic reactivity,[63] and the development of adverse mood states,[109,167] 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.[110] 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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