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The role of stress and the hypothalamic–pituitary–adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes

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The stress system coordinates the adaptive response of the organism to real or perceived stressors. The main components of the stress system are the corticotropin-releasing hormone (CRH) and locus ceruleus-norepinephrine/autonomic (LC/NE) systems and their peripheral effectors, the hypothalamic–pituitary–adrenal (HPA) axis, and the limbs of the autonomic system. Activation of the stress system leads to behavioral and peripheral changes that improve the ability of the organism to adjust homeostasis and increase its chances for survival. Thus, CRH and the LC/NE system stimulate arousal and attention, as well as the mesocorticolimbic dopaminergic system, which is involved in anticipatory and reward phenomena, and the amygdala, which are responsible for the generation of fear. Hypothalamic CRH plays an important role in inhibiting gonadotropin-releasing hormone secretion during stress, while via somatostatin it also inhibits growth hormone, thyrotropin-releasing hormone and thyrotropin secretion, suppressing thus reproduction, growth and thyroid function. Glucocorticoids directly inhibit pituitary gonadotropin, growth hormone and thyrotropin secretion and make the target tissues of sex steroids and growth factors resistant to these substances. In addition, glucocorticoids stimulate hepatic gluconeogenesis, and inhibit or potentiate insulin actions on skeletal muscle and adipose tissue respectively, ultimately promoting visceral adiposity and the metabolic syndrome. Glucocorticoids also have direct effects on the bone, inhibiting osteoblastic activity and causing osteoporosis. Obese subjects with psychiatric manifestations ranging from those of melancholic depression to anxiety with perception of 'uncontrollable' stress, frequently have mild hypercortisolism, while carefully screened obese subjects with no such manifestations are eucortisolemic. The former may have stress-induced glucocorticoid-mediated visceral obesity and metabolic syndrome manifestations, which in the extreme may be called a pseudo-Cushing state that needs to be differentiated from frank Cushing syndrome. Stress-induced hypercortisolism and visceral obesity and their cardiovascular and other sequelae increase the all-cause mortality risk of affected subjects by 2–3-fold and curtail their life expectancy by several years.
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'*In human beings the mind governs the body, and health and illness depend on it.*'

Antiphon, Athens, 5th Century BC

Introduction

Both patients with depressive symptomatology and/or fully fledged melancholic depression and patients with central/visceral obesity associated with insulin resistance (metabolic syndrome) have marked increases in their cardiovascular morbidities and mortalities and a shortening of their life expectancies by several years.[1,2] Depressive symptomatology/melancholic depression have been linked to hypercortisolism since the early 1970s, while central/visceral obesity was associated with excess cortisol secretion more recently, in the early 1990s.[3–6] Co-morbidity of the two syndromes, ie. depressive symptomatology/depression and central, visceral obesity with insulin-resistance, is frequently observed, and these patients may need to be differentiated from those with frank endogenous Cushing syndrome, a rare but devastating condition (Figure 1). Such patients have been heuristically described by the term pseudo-Cushing's, because they frequently require differentiation from Cushing syndrome by means of several, ever-improving biochemical tests, such as the combined dexamethasone suppression/CRH stimulation test or the recombinant human interleukin-6 (IL-6) stimulation test.[7–9] It has been our experience that pseudo-Cushing patients represent only a small but substantial subgroup of patients with depressive symptomatology/depression and overt visceral obesity with insulin resistance, but that patients with either condition may develop varying manifestations of the metabolic

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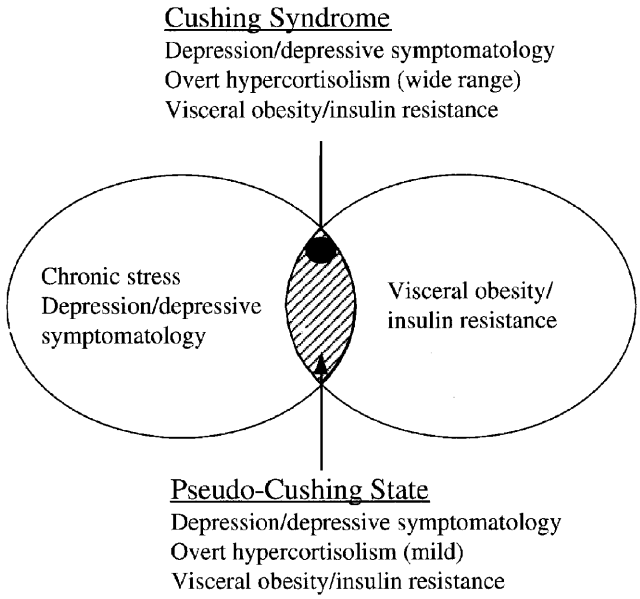

Figure 1 Venn diagram representing the overlapping populations of individuals with chronic stress/depressive symptoms and a hyperactive stress system *vs* those with visceral obesity and insulin resistance. The patients in the union represent a comorbidity syndrome which is frequently hard to differentiate from the much rarer endogenous Cushing's syndrome; they have been referred to by the appropriate term 'pseudo-Cushing state'.

syndrome, depending on genetic, developmental and/or environmental factors.

This brief review focuses mostly on the mechanisms through which the stress system produces endocrine and metabolic changes that lead to the development of the metabolic syndrome and its cardiovascular sequelae, and on how adipose tissue-specific hypersensitivity to glucocorticoids might also lead to visceral obesity associated with insulin resistance, in the absence of a hyperactive stress system. The latter is one of several potential explanations for the development of the metabolic syndrome in the great majority of centrally obese patients that have no biochemical hypercortisolism.

The stress system and its endocrine and metabolic effects

The hypothalamic–pituitary–adrenal (HPA) axis together with the sympathetic system mediates the effects of centrally perceived stress in the periphery of the body; the central nervous system (CNS) centers of the HPA axis and sympathetic system (consisting, respectively, of the parvicellular corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) neurons of the paraventricular nuclei of the hypothalamus, and the noradrenergic neurons of the locus ceruleus/norepinephrine (LC/NE) nuclei of the brain stem) innervate and stimulate each other and have both a baseline circadian and stress-related activity[10] (Figure 2). In an individual subject, the secretion of the end-product of the HPA axis, cortisol, is kept within an 'optimal' time-integrated narrow range, which is quite stable from day-to-day.[11] This is accomplished by a tightly regulated servo-control system which prevents excessive and prolonged cortisol secretion that would be detrimental to the organism; in contrast to the narrow intra-individual range, the inter-individual range is the normal human population is quite broad.

Excessive and sustained cortisol secretion or chronic administration of pharmacologic doses of glucocorticoids (endogenous or exogenous Cushing syndrome, respectively) have been long associated with depression, hypertension, osteoporosis, immunosuppression and the entire spectrum of the Metabolic Syndrome, including visceral obesity, insulin resistance, dyslipidemia, dyscoagulation and hypertension, along with their morbid sequelae of atherosclerosis and cardiovascular disease[7,12–14] (Figure 2, Table 1). Each of these manifestations could in theory be produced, despite the presence of normal, nonhyperfunctioning HPA axis, by tissue-specific hypersensitivity to glucocorticoids of, respectively, the amygdala or mesocorticolimbic system, cardiovascular system, bone, immune system or adipose tissue.[15]

There are marked clinical, physiologic and biochemical similarities between acute stress and the melancholic depression syndrome.[3,4,10] Both conditions are indeed associated with a hyperactive HPA axis and LC/NE system and, hence, increased CRH, cortisol and catecholamine secretion, and consequent inhibition of the growth, thyroid and reproductive axes, suppression of the immune system and elevation of catecholamine-stimulated interleukin-6 (IL-6) concentrations.[16] In the case of melancholic depression, the hyperactivity of the stress system can be chronic or in repeated bouts, which could potentially produce the long-term consequences of Cushing's syndrome (Figure 2, Table 1). Indeed, prior history of melancholic depression was associated with marked osteoporosis in premenopausal women carefully matched for body mass index (BMI) to premenopausal controls.[17] Furthermore, patients with depressive symptomatology, including properly diagnosed melancholic depression, have a markedly decreased life expectancy due to increased mortality from primarily cardiovascular causes (relative risk 2–3 over gender- and age-matched controls).[18–20] Although only 10–15% of the adult population may fulfill the criteria for major depression, it is quite likely that there is a continuum of depressive symptomatology from dysthymia to melancholia, with only a proportion of the patients qualifying as melancholics.

Recently, Rosmond *et al*[21] examined a large unselected population of 53 y old men by obtaining a detailed history, performing physical examinations including anthropometric measurements, and by obtaining a series of diurnal salivary cortisol determi-

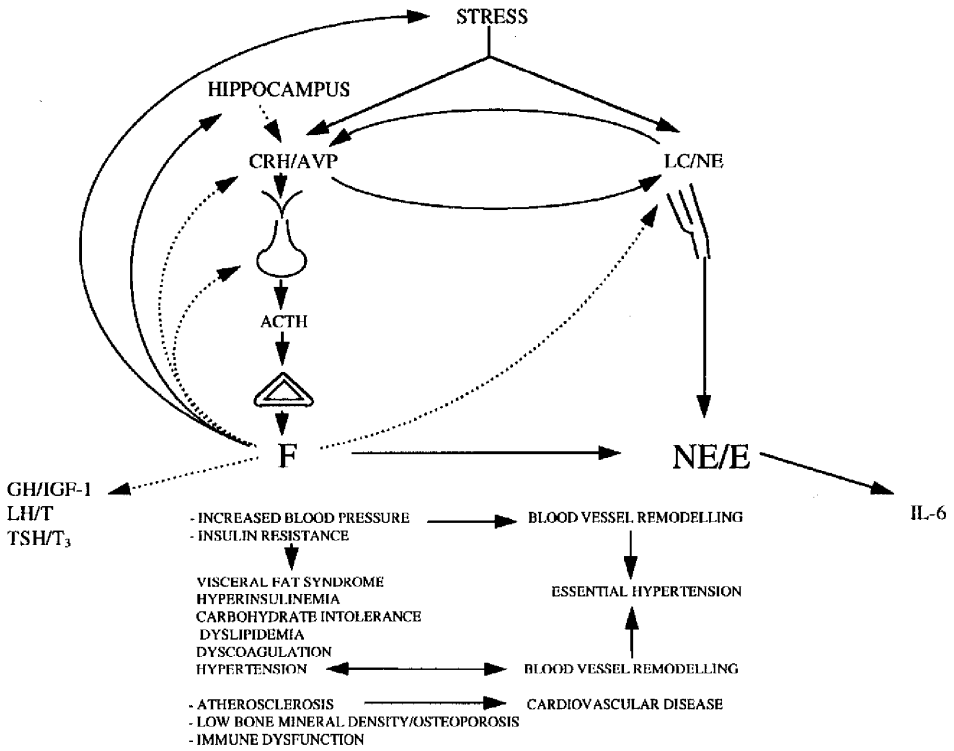

Figure 2 A schematic representation of the stress system. The CRH/AVP neurons are reciprocally connected with the noradrenergic neurons of the LC/NE system in a positive reverberatory circuit. The HPA axis is controlled by several negative feedback loops, which tend to normalize the time-integrated secretion of cortisol yet glucocorticoids stimulate the amygdala and, hence, the fear center. Activation of the HPA axis leads to suppression of the GH/IGF-1, LH/testosterone and TSH/T3 axes; activation of the sympathetic system increases IL-6 secretion. Chronic increases in cortisol, catecholamines and IL-6 and chronic suppression of the GH/IGF-1, LH/T and TSH/T3 axes provide a hormonal milieu which is conducive to the development of visceral obesity, hypertension, atherosclerosis, osteoporosis and immune dysfunction; their sequelae are increased morbidity and mortality of mostly cardiovascular etiology (from Chrousos and Gold.[14]) *Symbols:* straight lines indicate stimulation; dashed lines indicate inhibition. *Abbreviations:* CRH = corticotropin-releasing hormone; AVP = arginine-vasopressin; LC/NE = locus ceruleus/norepinephrine system; GH = growth hormone; IGF-1 = insulin like growth factor-1; LH = luteinizing hormone; T = testosterone; TSH = thyrotropin; T3 = triiodothyronine; F = cortisol; NE = norepinephrine; E = epinephrine; IL-6 = interleukin-6.

nations in parallel with an acceptable measure of stress perception and by performing a low dose overnight dexamethasone suppression test. The results revealed that the increases in blood pressure and body mass index, earlier seen in Cushing's syndrome as a result of hypercortisolism, could also be seen in a general population of non-Cushingoid middle-aged men in correlation with the degree of stress perception and stress-related cortisol secretion.

A crucial observation made upon the initial analysis of these data is modeled in Figure 3A. A 'nonstressed' HPA axis was characterized by an increased variance mostly due to a wide circadian variation, with distant morning zeniths and evening nadirs, a discrete but small lunch-induced cortisol peak and an appropriate suppression of the morning cortisol levels in response to low-dose dexamethasone; a chronically stressed HPA axis, on the other hand, was characterized by a decreased variance mostly due to evening nadir elevations and morning zenith decreases, a large lunch-induced cortisol response and an inadequate suppression of morning cortisol by overnight dexamethasone. These findings suggest chronic hypersecretion of CRH in chronically stressed individuals and a reset of their HPA axis, as previously suggested. We expect that the total time-integrated cortisol secretion would be increased in these individuals. However, in the presence of a properly functioning glucocorticoid negative feedback system, around-the-clock cortisol secretion would be minimized to the greatest possible extent and, hence, would be less indicative of a chronically stressed HPA axis than the other features included in Table 1.

The ability of the glucocorticoid negative feedback system to limit the production of cortisol during stress can be impaired by early life stress, history of chronic emotional/physical stress and old age.[22–24] Glucocorticoid-induced hippocampal neuron damage and deficient transmission of suprahypothalamic negative feedback has been proposed as a major mechanism mediating this phenomenon[25] (Figure 2, Table 1). Indeed, in patients with melancholic depression, the 24 h urinary free cortisol excretion increases with age, while studies of the HPA axis in ageing populations that include persons with chronic emotional or physical diseases, have shown progressive elevations of evening plasma cortisol concentrations with age. Interestingly, carefully screened aged subjects devoid of physical or emotional illness have normal HPA axis activity through their 90s.[26,27]

The question is often raised as to whether an altered daily cortisol secretion variance can produce the somatic

Table 1 Physiologic/somatic consequences of chronic stress system activation/target tissue effects (modified from Chrousos and Gold[14])

HPA axis cortisol	*Locus ceruleus/norepinephrine catecholamines, IL-6*
CNS effects	
+ Hippocampal negative feedback impairment	
+ Potentiation of amygdala actions/fear	+ (Catecholamines)
+ Mesocorticolimbic dopaminergic system dysfunction	
− Leptin actions	
− GH/IGF-1	
− LH/T/E_2	
− TSH/T_3	− (IL-6)
Increased blood pressure	
+ Vasoconstrictor systems	
Catecholamines/angiotensin 2	+ (Catecholamines)
Arginine-vasopressin/endothelin	
− Vasodilatory systems	
Kallikrein/prostacyclin	
Nitric oxide synthase/inflammatory cytokines	
+ Salt retention	
+ Renin substrate	+ Renin (catecholamines)
Visceral fat syndrome	
Insulin resistance	
+ Gluconeogenesis	+ (Catecholamines)
− Peripheral glucose disposal	
+ Insulin concentrations	
+ Visceral fat cell growth/function	
+ Carbohydrate intolerance	
+ Cholesterol, LDL, small dense LDL, FFA, triglycerides	
− HDL	
+ Coagulation processes	+ (IL-6)
− Thrombolytic processes	
− Insulin-induced vasodilation causing hypertension	
+ Impaired insulin secretion	
Atherosclerosis/cardiovascular diseases	+ (IL-6 proinflammatory activity)
Low bone mineral density/osteoporosis	
− Osteoblastic activity	+ Osteoclastic activity (IL-6)
Immune dysfunction	
− IL-12, TH_1	+ IL-4, IL-10, IL-13, TH_2

+, stimulation; −, inhibition; CNS, central nervous system; HPA axis, hypothalamic–pituitary–adrenal axis; GH/IGF-1 = growth hormone/IGF-1; LH/T/E_2, luteinizing hormone/testosterone/estradiol; TSH/T_3, thyrotropin/triiodothyronine; LDL, low density lipoprotein; FFA, free fatty acid; HDL, high density lipoprotein; IL, interleukin; TH_1, T helper 1; TH_2, T helper 2.

sequelae of chronic hypercortisolism. Despite the attempt of the brain to correct for the evening excess cortisol production by suppressing the morning cortisol surge, it is possible that no such complete correction is attained and the body tissues are overexposed to cortisol. Similarly, increased evening exposure to cortisol could be detrimental on its own, in spite of an adequate correction of time-integrated cortisol secretion. We recently reported an adult man with Carney complex, a rare form of primary Cushing's syndrome treated in childhood with unilateral adrenalectomy.[28] Although his 24 h urinary free cortisol excretion remained normal for many years, he developed severe osteoporosis, possibly as a result of constant exposure of his bones to normal, albeit 'flat', levels of plasma cortisol.

Tissue sensitivity to glucocorticoids

The majority of patients with visceral obesity and insulin resistance have no depressive symptomatology and an entirely normal HPA axis.[29,30] The apparent increase of the input of the stress system in such individuals, if any, might be a result of increased glucocorticoid sensitivity at the level of target tissues, namely the visceral fat and/or the cardiovascular system. Panarelli *et al*[31] recently studied a group of young adult males, aged 18–40 y. They focused their studies on a previously described polymorphism of the glucocorticoid receptor, which was earlier associated with hypertension and visceral obesity.[32,33] This polymorphism was associated with an increased blanching skin reaction to butesonide, but not with systemic blood pressure, plasma biochemistries known to be affected by glucocorticoids (Table 1), the affinity or concentration of glucocorticoid receptors in cultured leukocytes, or the dexamethasone-induced inhibition of lysozyme production by cultured leukocytes *in vitro*. Thus, these authors found one hypersensitive dose–response curve to glucocorticoids-skin vasoconstriction, but not others (Figure 3B). The finding of the correlation between an undefined nonstructural polymorphism of the glucocorticoid receptor gene and a hypersensitive curve suggests that tissue-limited hypersensitivity to glucocorticoids, or its mirror image, glucocorticoid resistance, exist as earlier hypothesized on a theoretical basis.[15]

Huizenga *et al*[34] recently demonstrated that another polymorphism of the glucocorticoid receptor, which

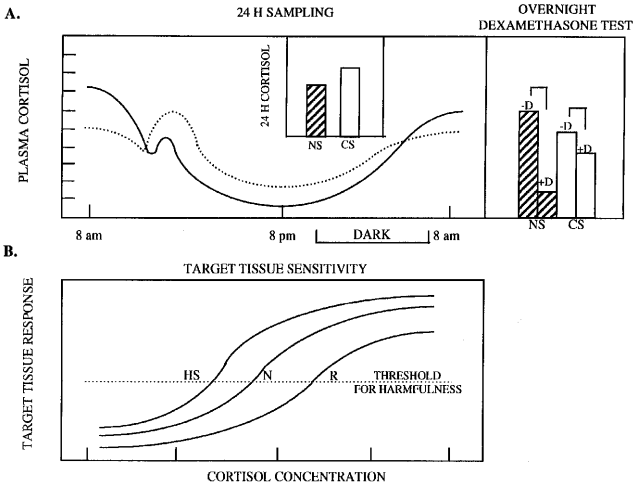

Figure 3 (A) (Left) Circadian pattern of cortisol secretion in nonstressed (NS) and chronically stressed (CS), individuals. Note the blunting of the circadian rhythm in the latter, along with an augmented cortisol elevation in response to lunch. (Right) Cortisol response to a low dose of overnight dexamethasone (D). Note the increased suppressibility of nonstressed individuals *vs* chronically stressed subjects. (B) Dose–response curves of target tissue responses to cortisol: N = normal; HS = hypersensitive; R = resistant. The interrupted horizontal line represents a threshold effect beyond which long-term harm is done (Figure 1, Table 1). Depending on the shift at the dose–response curve to the left or right one would expect harmful or protective effects. (From Chrousos and Gold[14]).

we described earlier,[35] was present in 6% of normal Dutch men and associated with a significantly greater cortisol suppression by dexamethasone, a higher BMI and a lower bone mineral density (BMD) in polymorphism carriers than in noncarriers. More recently, Walker *et al*[36] reported correlation of increased dermal glucocorticoid sensitivity with relative hypertension, insulin resistance and hyperglycemia. Interestingly, the same high glucocorticoid sensitivity subjects also had enhanced secretion of cortisol and impaired conversion of cortisol to inactive metabolites (cortisone and 5β-dihydrocortisol). Finally, experimental overexpression of glucocorticoid receptors in the pancreatic cells of transgenic mice caused defective insulin secretion and carbohydrate intolerance,[37] changes observed in patients with Cushing's syndrome as well.[12] Our opinion is that within the human population there is variation in target-gene-specific responsiveness to glucocorticoids, which is the result of not only mutations in the gene of the glucocorticoid receptor, but also in genes that are involved in the glucocorticoid signal transduction pathway, including cortisol metabolizing enzymes, heat shock proteins, immunophilin, coactivators/corepressors, etc.[38] These normal variations could be harmful or protective, depending on the gene and the direction of the variation.

Summary

Stress- and depression-induced hypercortisolism and central obesity are associated with varying degrees and patterns of the metabolic syndrome, and their sequelae, and are common phenomena of major epidemiologic and fiscal importance. The complex picture of these largely interrelated phenomena has been slowly unraveling to give us an ever clearer biological view and to provide us with the potential to intervene rationally to both prevent and treat. Thus, appropriate changes in lifestyle and the treatment of emotional disorders will help prevent and treat the devastating organic sequelae of emotional stress and visceral obesity. The introduction of modern therapeutic methods in depression has already led to a marked lowering of all-cause morbidity and mortality in this condition.

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