ELSEVIER

REVIEW

Role of stress in the pathogenesis of the metabolic syndrome[☆]

Roland Rosmond*

Lundvägen 6, S-433 64 Sävedalen, Sweden

Summary Excess body fat, obesity, is one of the most common disorders in clinical practice. In addition, there is a clustering of several risk factors with obesity, including hypertension, glucose intolerance, diabetes mellitus, and hyperlipidemia, which is observed more frequently than by chance alone. This has led to the suggestion that these represent a single syndrome and is referred to as the Metabolic Syndrome. A growing body of evidence suggests that glucocorticoid secretion is associated with this complex phenotype. Continuously changing and sometimes threatening external environment may, when the challenge exceeds a threshold, activate central pathways that stimulate the adrenals to release glucocorticoids. In this review, we will discuss how such processes mediate a pathogenetic role in the Metabolic Syndrome.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

The idea that frequent or persistent stimulation of the hypothalamic–pituitary–adrenal (HPA) axis may constitute a base for pathophysiological consequences in the periphery of the body stems from the central role played by the HPA axis in the homeostatic processes. Although biologically plausible, this complex hypothesis has been difficult to study in humans (Chrousos and Gold, 1998), presumably because of several inherent obstacles. Subsequently, studies in humans of the impact of environmental factors on the HPA axis have provided inconsistent findings (Brantley et al., 1988; Cummins and Gevirtz, 1993).

The presence of a continuously changing and sometimes threatening external environment may, when the challenges exceed a threshold, activate the HPA axis through unknown central afferent pathways that stimulate the hypothalamus to release multiple corticotropin (ACTH) secretagogues, corticotropin-releasing hormone (CRH) and arginine vasopressin being the most important (DeBold et al., 1984; Taylor and Fishman, 1988). The resulting increase in plasma cortisol assists to sustain the internal environment. Endocrine feedback

regulation balances the central afferent signals, which allows the HPA axis to keep cortisol levels within an optimal range (Dallman et al., 1994).

Excessive and protracted cortisol secretion is the result of a frequently evoked HPA axis, either by environmental factors or by intrinsic factors. The condition of cortisol hypersecretion causes diseases such as hypertension, osteoporosis and depression (Chrousos and Gold, 1998). In addition, elevated cortisol levels contribute to the development of the entire spectrum of the Metabolic Syndrome, including visceral obesity, insulin resistance and dyslipidemia as well as the kinds of cardiovascular comorbidities that result (Björntorp, 1993).

2. The concept of stress

2.1. Milieu intérieur, homeostasis and the general adaptation syndrome

Stress is a ubiquitous term with no universally accepted definition. The origin of the concept of stress in biology and medicine is unknown. Investigations of stress rise from the recognition by Claude Bernard in 1878, that all living processes exist in a state of dynamic internal physiologic equilibrium ('milieu intérieur'), formed by organic liquid that surrounds all of the tissue elements. He wrote: "All the vital mechanisms, varied as they are, have only one object, that of preserving constant conditions of life in the internal environment" (Bernard, 1878). Walter B. Cannon explained the mechanisms of maintaining physiological factors within certain limits and coined the term 'homeostasis' and defined it as 'the coordinated physiological process which maintains most of the steady states in the organisms' (Cannon, 1939). He described a 'critical stress' level as one that produces a 'breaking strain' that results in failure to maintain homeostasis, and by that, adopting the terms 'stress' and 'strain' as they are used in physics. Many of his experiments were conclusive and relevant to current understanding of the role of catecholaminergic systems in stress responses. He also explained the emotional responses of rage and fear, which he called 'fight or flight' responses. Hans Selye extended Cannon's idea of homeostasis to include the responses mediated by the HPA axis and proposed a new concept of stress, the 'general adaptation syndrome, or GAS'; a single stereotypic response elicited by any demand upon the body (Selye, 1956). For scientific purposes, he defined stress 'as the state that manifests itself by the GAS'. Selye popularized stress as a scientific and medical idea,

and his stress theory remains popular. By 1982, Selye's International Institute of Stress had indexed more than 200,000 publications about different aspects of the stress concept (Selye, 1982).

As research uncovered a number of systems that participate in stress responses, it became less clear if a nonspecific response truly existed. John W. Mason (Mason, 1971, 1975) and others disputed Selye's idea of a nonspecific and stereotyped stress response, as the HPA axis is capable of responding differently to different stressors (Mason, 1971). Mason suggested that the similarities in neuroendocrine responses to different physical stressors derived from the fact that all the stressors used in Selye's experiments caused emotional distress, resulting in similar endocrine response.

2.2. Current conceptions of stress

In more recent decades, the central neurohormonal response patterns to stress have been greatly elicited throughout studies in both animals and humans (Henry, 1992; Folkow, 1993, 1997). These studies have also illustrated that the individual differences in response pattern are a product of both the stressful stimulus as well as the capability to habituate or adapt to the situation, so called coping (Lazarus, 1993).

Much of the current conceptualization of the stress response has been pioneered by Chrousos and Gold (1992), who define stress as a state of disharmony or of threatened homeostasis, evoking adaptive responses when the threat to homeostasis exceeds a threshold. The authors have postulated that two principal components in the hypothalamus and the brainstem mediate the stress response: the CRH-neurons and the locus coeruleus-norepinephrine/sympathetic system. An increased or decreased activity in this 'stress system' produces abnormal levels of mainly cortisol, norepinephrine and epinephrine, and contributes to several disorders such as depression, anxiety, and hypothyroidism. Chrousos and Gold thus explain stress-related disorders circularly in terms of maladaptiveness, to some extend similarly to Selye's doctrine of 'diseases of adaptation'.

Since homeostatic systems in the human body are subject to frequent changes across an operating range in response to environmental factors, Sterling and Eyer (1988) coined the term allostasis and defined it as the ability of the body to increase or decrease vital functions to a new state. However, the concept of allostasis does not match the long-term effect of repeated disruptions of

a homeostatic system, which tends to result in drifting of the absolute value to a new level that can predispose an individual to disease. Consequently, McEwen (1998) introduced the term allostatic load to define the impact of 'wear and tear' on a number of bodily functions that result from 'chronic over-activity or underactivity of the allostatic systems'.

From the work and ideas of Chrousos, Gold and McEwen we glean the following definitions (to be used throughout this overview): *stress* is a state of threatened homeostasis, and *chronic stress* is the long-term repeated disruption of a homeostatic system.

3. Defining a stressor

A major difficulty in the study of stress and stress response is the varying conceptions of a stressor. Animal models of stress have included such stressors as induced hunger, exposure to cold, physical restraint, exposure to a socially dominant member of the same species, inescapable electric shocks, or near drowning (McEwen and Stellar, 1993). Human stressors are generally more broadly defined to also include complex life events such as adversity in relationship, health, work, finances, and with social structure. Although there is some evident that psychological stress activates the same pathways as observed in animal models, caution must be taken not to overgeneralize.

4. Metabolic syndrome: definition and epidemiology

In recent years, scientists have recognized that some risk factors for cardiovascular disease and type 2 diabetes cluster together in certain people (Björntorp et al., 1971; Björntorp, 1988; Reaven, 1988). This clustering of multiple metabolic risk factors is called the Metabolic Syndrome. These risk factors include elevated insulin levels (insulin resistance), visceral obesity, high levels of trigly-cerides and low levels of high-density lipoprotein cholesterol as well as hypertension. In addition to insulin resistance, visceral obesity is a key contributor to the development of the Metabolic Syndrome.

The location of body fat has emerged as an important predictor of the health hazards of obesity. Sites of body fat predominance are easily measured by the ratio of waist-to-hip circumferences. High ratios are associated with higher risks for diabetes, hypertension, heart disease, or their associated risk factors (Rosmond, 2001).

A WHO expert committee has determined a working definition of the Metabolic Syndrome to include glucose intolerance, or diabetes mellitus and/or insulin resistance together with two or more of the following components: raised arterial pressure $\geq 140/90$ mm Hg, raised plasma trigly-cerides ≥ 1.7 mmol and/or low HDL-cholesterol < 0.9 mmol l^{-1} men; < 1.0 mmol l^{-1} women: visceral obesity (waist-to-hip ratio > 0.90 men; > 0.85 women) and/or body mass index (BMI) > 30 kg m^{-2}: and finally, microalbuminuria (WHO, 2000).

Data from the European Group for the study of Insulin Resistance and the Danish Twin Register has shown that insulin resistance correlates closely with the various components of the Metabolic Syndrome, and that the prevalence of the syndrome is approximately 16% among Caucasians (Beck-Nielsen, 1999). However, comparison of the prevalence of the Metabolic Syndrome across different countries is difficult as there are different age structures of the population, definitions are not the same and surveys may not be population-based. In a large family study of type 2 diabetes in Finland and Sweden, the Metabolic Syndrome was seen, in women and men, respectively, in 10 and 15% of subjects with normal glucose tolerance, 42 and 64% of those with impaired fasting glucose/impaired glucose tolerance, and 78 and 84% of those with type 2 diabetes (Isomaa et al., 2001). Moreover, the risk for coronary heart disease and stroke was increased threefold in subjects with the syndrome (Isomaa et al., 2001). In another study from Finland, the Metabolic Syndrome, defined as a clustering of dyslipidaemia (hypertriglyceridaemia, low HDL-cholesterol, or both) and insulin resistance (abnormal glucose tolerance, hyperinsulinaemia, or both) was present in 17% of men and in 8% of women (Vanhala et al., 1997).

Significant associations are seen between excess body fat and the development of the Metabolic Syndrome. In the British Regional Heart Study, nearly 50% of the obese men showed the 'full metabolic syndrome' (hypertension, hyperglycaemia and dyslipidaemia) (Wannamethee et al., 1998). Obesity and consequently the Metabolic Syndrome are relatively common in Europe, especially in Southern European countries. For instance, even in the Cretan low risk population of Spili, hypertension, diabetes, obesity, and hypercholesterolaemia were found to be at least as prevalent as in Sweden (Koutis et al., 1992).

Obesity and the Metabolic Syndrome is an escalating problem in the US; more than half of all US adults are considered overweight or obese (Must et al., 1999). In a large cohort, the prevalence of a cluster of metabolic abnormalities (high blood glucose, high blood pressure, low HDL-cholesterol, and high triglycerides) was analyzed and its impact on cardiovascular disease mortality in 22,561 men and 18,495 women (Trevisan et al., 1998). The prevalence of the full cluster of metabolic abnormalities was low in the population as a whole, with only 3.0% of men and 3.4% of women exhibiting the full cluster of abnormalities (Trevisan et al., 1998). In post-menopausal American Caucasian women, the simultaneous presence of hypertension, dyslipidemia, and abnormal glucose tolerance, was around 8% (Yarbrough et al., 1998). Neither of these two studies used the recommended WHO definition of the Metabolic Syndrome to include visceral obesity. Based on the evidence of increasing prevalence of obesity and obesity-related comorbidities, the prevalence of the Metabolic Syndrome in the US is likely to be much higher. This was recently confirmed in 3224 Caucasian men and women attending Framingham Offspring Study (Meigs et al., 2003). Among these subjects, the age- and sex-adjusted prevalence of the metabolic syndrome was 24% by WHO criteria (Meigs et al., 2003).

Nationally representative data for countries in the Eastern Mediterranean Region is not well documented. Nevertheless, the limited data available indicate that the prevalence of the Metabolic Syndrome is rather high. In a Palestinian population, the age-adjusted prevalence of the Metabolic Syndrome as defined by the WHO was 17% (Abdul-Rahim et al., 2001).

Only limited prevalence data are available for Southeast Asian countries. Recent data suggest that at least 10% prevalence of type 2 diabetes, hypertension, and adverse lipid profiles in Hong Kong Chinese subjects (Lee et al., 2000).

5. Stress and insulin resistance

Although stressors can be distinguished in terms of the 'type' of stimulus (McEwen and Stellar, 1993), a key component of the stress response involves activation of the HPA axis. Together with the nervous system, they provide much of the extracellular control of specialized tissues to function as integrated organs. There is, however, no sharp distinction between the endocrine and nervous systems. In the hypothalamus and the pituitary there is a close connection between these two systems that integrates them into one control unit.

Neurons within the medial paraventricular nucleus of the hypothalamus (PVN) synthesize CRH, and project to median eminence, releasing CRH into the anterior pituitary via the hypophyseal-portal vessels to stimulate hormone production and secretion, among others ACTH. In addition, catecholamines play an important role in the regulation of the PVN neurons (Dallman, 1993; Herman and Cullinan, 1997). High catecholamine levels enhance the HPA axis response, and the CRH seems to stimulate sympathetic outflow (Chrousos and Gold, 1998).

Since the early 1980s, a wealth of information has accumulated which illustrates that activation of the HPA axis leads to suppression of both the growth axis and the reproductive axis including an activation of the sympathetic system (Chrousos, 1998). Chronic increases in cortisol, catecholamines, and chronic suppression of the growth axis and the reproductive axis lead to a number of adverse health effects, and their sequelae resulting in increased morbidity and mortality.

Cortisol interferes at several levels of insulin action (Amatruda et al., 1985). In addition, cortisol inhibits insulin secretion from pancreatic β-cells (Lambillotte et al., 1997). In primary cultured adipocytes, synthetic glucocorticoids (dexamethasone) induce progressive insulin resistance by sequentially regulating multiple aspects of the insulin-responsive glucose transport system (Garvey et al., 1989). At early times, dexamethasone impairs insulin's ability to translocate intracellular glucose transporters (GLUT 4) to the cell surface (Garvey et al., 1989; Coderre et al., 1996). Some, but not all studies, indicate that glucocorticoids may increase hepatic glucose metabolism (Pagano et al., 1983; Wajngot et al., 1990). This diabetogenic effect of glucocorticoids is well characterized at least in animal models (Dallman et al., 1993). In skeletal muscle, cortisol inhibits the glycogen synthase (Holmäng and Björntorp, 1992). Recent data indicate that subjects with insulin resistance do have an increased number of glucocorticoid receptors in muscle (Reynolds et al., 2002).

In summary, initially hyperglycemia is accompanied by an increased insulin response to a glucose load, but eventually β-cell response becomes insufficient, and the unopposed actions of stress-related counter regulatory catabolic hormones (cortisol, catecholamines) serve to exacerbate the metabolic disturbances and contribute to the biochemical changes seen. This simplified

account provides a framework within which the association between stress and insulin resistance can be understood.

6. Stress and visceral obesity

Cortisol regulates adipose-tissue differentiation, function, and distribution, and in excess, causes visceral obesity. Visceral obesity is one of the key components of the Metabolic Syndrome. Clinical observations have long suggested a connection between visceral obesity and Cushing's syndrome. In fact, subjects with visceral obesity share many of the metabolic, hormonal, circulatory, and behavioral findings observed in Cushing's syndrome.

Circulating cortisol is largely bound to plasma proteins. The major binding proteins are albumin and corticosteroid-binding globulin, and less than 5% of the plasma cortisol is unbound (Dunn et al., 1981). Glucocorticoids exert their cellular action by complexing with a specific cytoplasmic glucocorticoid receptor (GR), which in turn translocates to the nucleus and binds to specific sites on chromatin. GR belongs to the superfamily of nuclear transcription factors (DeRijk et al., 2002; Rosmond, 2002).

Since cortisol affects so many physiological processes, it is not realistic to try to formulate a unifying definition of cortisol action. In addition to effects on glucose metabolism, cortisol inhibits amino acid uptake and protein synthesis in peripheral tissues (muscle, skin, bone). Cortisol acutely activates lipolysis in adipose tissue (Björntorp, 1996). In adrenalectomized animals, the lipolytic activity and, consequently, plasma free fatty acid levels are reduced (York, 1996).

Cortisol also exerts chronic effects on lipid metabolism. One of the most striking in humans is the centralization of body fat seen in Cushing syndrome, exhibited as severe truncal obesity. Excess cortisol promotes the activity of lipoprotein lipase (LPL), the primary enzyme responsible for conversion of lipoprotein triglyceride into free fatty acids and accumulation of triglycerides in adipocytes (Björntorp, 1996). The density of GRs, assessed by ligand binding technique (Rebuffe-Scrive et al., 1985) and hybridization technique with GR cRNA probes (Rebuffe-Scrive et al., 1990), are particularly high in intraabdominal adipose tissue as compared to other regions. Furthermore, the antilipolytic action of insulin during the prevailing hyperinsulinemic state causes a blunted lipid mobilization, resulting in a condition with increased lipid accumulation (Björntorp, 1996). Moreover, in the presence of insulin, cortisol has a marked stimulatory effect on LPL activity in human adipose tissue in vitro (Ottosson et al., 1994). This effect involves both an increased level of LPL mRNA, leading to increased relative LPL synthesis, and additional posttranslational regulation.

7. Stress and the cardiovascular system

The cardiovascular system is regulated in a complex manner, with compensatory adjustments in response to various stimuli (Björntorp et al., 2000). Hypertension is a disease that typically develops over years or decades. The natural history of hypertension is characterized by not only increasing blood pressure, but also is accompanied by a progressive rise in systemic vascular resistance (SVR) (Folkow, 1982). The structural autoregulation theory of hypertension, originated by Dr Folkow, is a cascading pathophysiological adaptation that helps explain why hypertension becomes a disease of elevated SVR. However, the unresolved question is what causes an individual's blood pressure to initially rise from normotensive levels, allowing the onset of pathophysiological processes. The answer to this question is likely multiple interacting factors, which vary across individuals.

The primary reason for considering stress as an etiologic factor relates to the influence of the sympathetic nervous system and neuroendocrine factors in hypertension, although high salt intake in some subjects may contribute through volume expansion (Björntorp et al., 2000). The principal hypothesis is that the stress-induced activation of hypothalamic, sympatho-hormonal regions occurs repeatedly over time, leading to cardiovascular adjustments that increase hypertension risk. Evidence relevant to this hypothesis derives from both animal and human experimental studies (Henry and Grim, 1990; Folkow, 1993; Björntorp et al., 2000). Complications such as myocardial infarction and stroke are not directly due to elevated pressures, but to the resulting structural changes in the heart and blood vessels. One of the structural consequences of hypertension, hypertrophy of the left ventricle, is the strongest predictor, other than advancing age, of cardiovascular morbidity and mortality (Gosse and Dallocchio, 1993).

A series of studies involving cynomolgus monkeys has been conducted to examine the effects of stress on coronary heart disease (Clarkson et al., 1987; Clarkson et al., 1989; Shively et al., 1990; Kaplan et al., 1996). Monkeys not only have similar coronary disease pathology to humans, but also exhibit many of the same behavioral characteristics that have

been cited as potential risk factors, such as competition, aggression, and social hierarchies (Marmot and McDowall, 1986; Ragland and Brand, 1988; Brunner et al., 1997). Current models of the effects of stress on cardiac pathophysiology suggest that activation of the sympathetic nervous system and the HPA axis increase the risk of cardiovascular events. This activation of hypothalamic, sympatho-hormonal regions results in a cascade of physiologic responses that may lead to myocardial ischemia, ventricular fibrillation, plaque rupture, or coronary thrombosis. The underlying pathophysiology relates to an increase of circulating catecholamines and cortisol, resulting in an elevated heart rate and blood pressure, coronary constriction, accumulation of lipid in the intima, and electrical instability (Skinner, 1985; Währborg, 1998).

8. The role of genes

Genes that are involved in the regulation of catecholamine function may be of particular importance because of the central role of catecholamines both as hormones and as neurotransmitters (see above). Four variants in the β_2-adrenergic receptor gene have been identified that cause changes in the encoded amino acids at residues 16 (Arg16Gly), 27 (Gln27Glu), 34 (Val34Met), and 164 (Thr164Ile) (Rosmond, 2003). The most frequent polymorphisms were Arg16Gly and Gln27Glu (Reihsaus et al., 1993). One of these, Arg16Gly, is reported to be associated with a fivefold increased agonist sensitivity of the β_2-adrenergic receptor (Large et al., 1997). More interestingly, a C-1291G polymorphism in the α_{2A}-adrenergic receptor gene has recently been found to be associated with cortisol escape from dexamethasone and elevated glucose levels (Rosmond et al., 2002b). This polymorphism of the α_{2A}-adrenergic receptor gene is located in the promoter or enhancer region, and could therefore alter gene expression and perhaps receptor density. The pathophysiology could involve an altered density of the α_{2A}-adrenergic receptor that destabilizes the sympathetic-HPA systems. This would provide an explanation for the observation of a subnormal cortisol response to dexamethasone (Rosmond et al., 2002b). Since the CRH-neurons are stimulated by catecholamines (al-Damluji and Francis, 1993), an altered gene expression and receptor density would alter the sensitivity to catecholamines in the hypothalamus. This notion is to some extent weakly supported by the statistically nonsignificant elevation in the diastolic blood pressure (Rosmond et al., 2002b).

An increased density of α_{2A}-adrenergic receptor has been reported in patients with essential hypertension (Mores et al., 1990).

The hypothalamus has extensive and complex neural connections. The CRH-neurons, found within the PVN, receive afferent regulatory signals from different parts of the brain. The CRH-neurons are excitatory influenced on by cholinergic and serotoninergic (5-HT) central pathways (Dinan, 1996). CRH-neurons are also activated by various cytokines such as tumor necrosis factor (TNF)-α (Reichlin, 1993). Inhibitory effects are exerted by γ-aminobutyric acid (GABA) (Calogero et al., 1988), which is the major inhibitory neurotransmitter in the vertebrate brain, and acts by binding to GABA$_A$ receptors.

The first biallelic TNF gene polymorphism in humans was detected in 1992 (Wilson et al., 1992), and involved a single base change from guanine to adenine at position -308 in the promoter region of the gene. In vitro experiments have demonstrated that the -308 variant increases transcriptional activation of the TNF gene (Wilson et al., 1997). The resulting increase of circulating levels of TNF is associated with elevated morning cortisol levels as well as elevated postprandial cortisol secretion (Rosmond et al., 2001), suggesting an amplification of responses to stimuli that normally induce cortisol release.

In addition to cytokines, complex interactions among various neurotransmitters play an important role in regulating HPA axis activity in response to a variety of physical and psychological stimulus. At present, it is thought that different brain regions act to integrate the sum of all stimuli perceived at a given moment, and then to convey this integrated information to the PVN to affect a coordinated HPA axis response (Herman and Cullinan, 1997). Many of these afferents utilize the inhibitory neurotransmitter GABA. Novel evidence suggests that an allelic variant in the GABA$_A\alpha$6 receptor subunit gene might lead to a dysfunction of the hypothalamic cortisol homeostasis-controlling mechanisms, resulting in elevated circulating cortisol levels (Rosmond et al., 2002a).

Negative feedback inhibition by cortisol interacting with neural control mechanisms is the means by which the brain keeps cortisol levels within physiological range (Dallman et al., 1994). In the late 1960s, with the classical work of Dr McEwen and colleagues, it became clear that the hippocampus had the highest density of GRs in the brain. Occupancy of GRs by cortisol or corticosterone serves to inhibit activity in the HPA axis. In the mid-1980s, Dr de Kloet and colleagues described that there are, in fact, two types of

corticosteroid receptors in the brain; mineralocorticoid receptors, which are saturated by basal levels of cortisol, and GRs, which are saturated only during peaks of the circadian rhythm and during stress (Sapolsky et al., 1986; Joels and de Kloet, 1994).

Studies with transgenic mice in which antisense RNA complementary to the 3′-noncoding region of the GR mRNA had been introduced was followed by reduced GR capacity and function, profound

behavioral changes and elevated plasma ACTH and corticosterone concentrations in response to stress (Pepin et al., 1992; Montkowski et al., 1995). In humans, several polymorphisms of the GR gene, which might have an impact on cortisol sensitivity, have been reported (DeRijk et al., 2002; Rosmond, 2002). Among these, the *Bcl*I polymorphism was identified by Southern blotting using human GR cDNA-specific probes, which identified two alleles with fragment lengths of
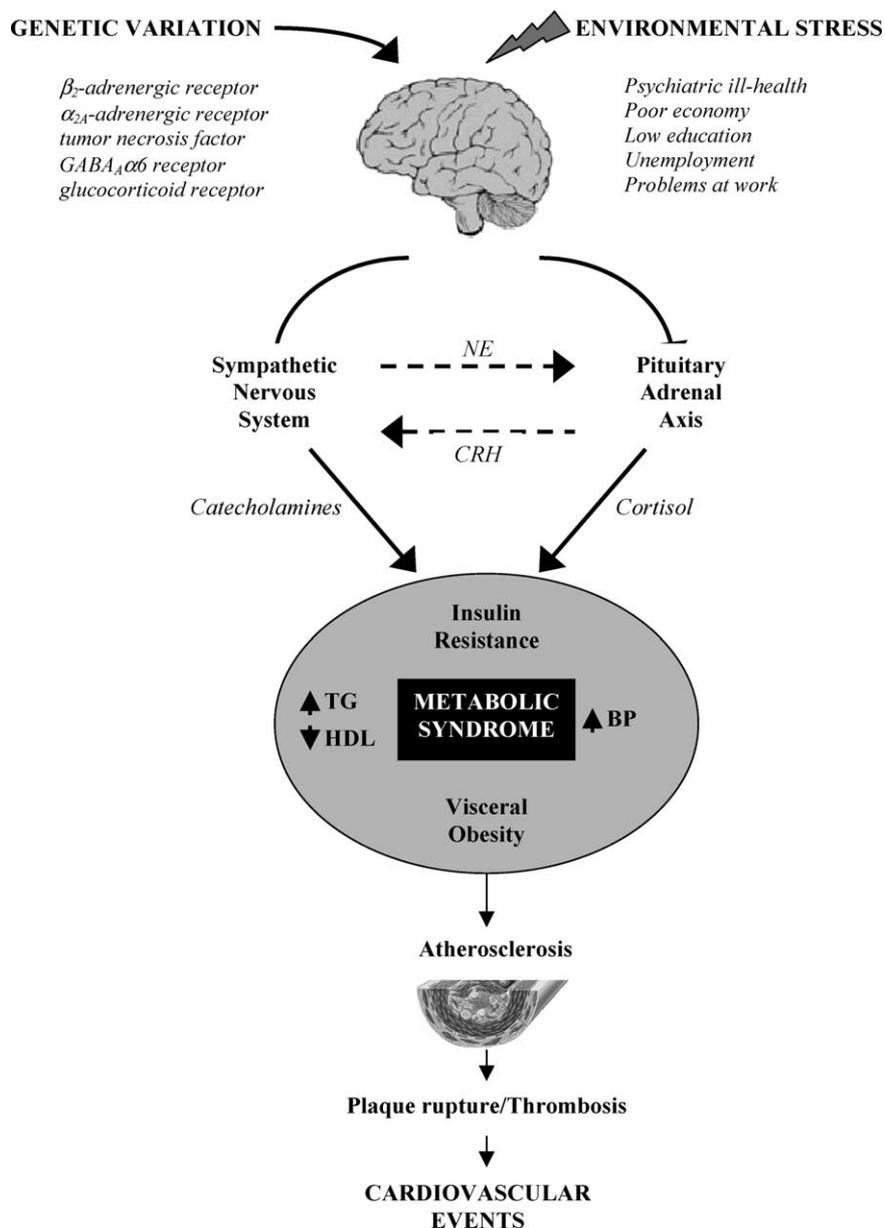

Figure 1 The CRH-neurons are reciprocally connected with the noradrenergic neurons of the sympathetic nervous system in a positive reverberatory circuit. Chronic increases in catecholamines and cortisol lead to insulin resistance, visceral obesity, high levels of triglycerides and low levels of high-density lipoprotein cholesterol as well as hypertension and their sequelae resulting in increased morbidity and mortality. Common genetic variants and environmental factors may impact the development of atherosclerosis at multiple levels through influences on visceral obesity, glucose and lipoprotein metabolism, and vascular function.

4.5 and 2.3 kb (Rosmond, 2002). This *Bcl*I polymorphism has been associated with elevated cortisol concentrations in response to metabolic stress (Rosmond et al., 2000). This was further documented by association of the *Bcl*I polymorphism with abdominal obesity (Rosmond et al., 2000), elevated fasting insulin and HOMA insulin-resistance index (Rosmond, 2002), and development of an atherogenic profile (Ukkola et al., 2001). Recently, the *Bcl*I polymorphism of the GR gene has been identified as a G-to-C substitution in intron 2, 646 nucleotides downstream from exon 2 (Fleury et al., 2003). These findings offer the use of methods, which are less labor-intensive than Southern blotting to genotype and, thus, facilitate screening of large groups.

9. Summary and conclusions

The human body holds many effector systems including the sympathetic nervous system and the HPA axis for maintaining homeostasis and to connect the brain with the periphery. Overall these systems interact both indirectly and directly (Björntorp et al., 2000). The HPA axis determines most of the acute and prolonged effects of stressors. The secretory end product of the HPA axis, cortisol, is kept within an optimal range through the feedback action of cortisol interacting with neural control mechanisms. Distressing events or situations evokes these two pathways of the stress response. However, each person's unique combination of heredity, life experience, personality, and ability to cope are all involved in the perception of an event and the meaning attached to it. Rather than confronting life-threatening stressors, life today centers around events that hold symbolic meaning; an upcoming test, a disagreement with a friend, or the boredom of a job.

Individuals with persistent psychosocial and socio-economic handicaps such as anxiety and depression, poor economy, low education and unemployment are more likely to suffer from frequent challenges of the HPA axis. In fact, socio-economic inequality and low educational level have recently been shown to be associated with elevated stress-related cortisol secretion (Rosmond and Björntorp, 2000). Thus, psychosocial and socio-economic impairments preceded by genetic variants that result in a disruption of central regulatory systems all adds up to less coping ability, followed by insulin resistance, visceral obesity, and cardiovascular diseases (Fig. 1).

References

Abdul-Rahim, H.F., Husseini, A., Bjertness, E., Giacaman, R., Gordon, N.H., Jervell, J., 2001. The metabolic syndrome in the West Bank population: an urban-rural comparison. Diabetes Care 24, 275-279.

al-Damluji, S., Francis, D., 1993. Activation of central alpha 1-adrenoceptors in humans stimulates secretion of prolactin and TSH, as well as ACTH. Am. J. Physiol. 264, E208-E214.

Amatruda, J.M., Livingston, J.N., Lockwood, D.H., 1985. Cellular mechanisms in selected states of insulin resistance: human obesity, glucocorticoid excess, and chronic renal failure. Diabetes Metab. Rev. 1, 293-317.

Beck-Nielsen, H., 1999. General characteristics of the insulin resistance syndrome: prevalence and heritability. European Group for the study of Insulin Resistance (EGIR). Drugs 58, 7-10 discussion 75-82.

Bernard, C., 1878. Leçons sur les Phénomènones de la Vie Communs aux Animaux et aux Végétaux. Ballière, Paris.

Björntorp, P., 1988. The associations between obesity, adipose tissue distribution and disease. Acta Med. Scand. Suppl. 723, 121-134.

Björntorp, P., 1993. Visceral obesity: a civilization syndrome. Obes. Res. 1, 206-222.

Björntorp, P., 1996. The regulation of adipose tissue distribution in humans. Int. J. Obes. Relat. Metab. Disord. 20, 291-302.

Björntorp, P., Bengtsson, C., Blohme, G., Jonsson, A., Sjöström, L., Tibblin, E., Tibblin, G., Wilhelmsen, L., 1971. Adipose tissue fat cell size and number in relation to metabolism in randomly selected middle-aged men and women. Metabolism 20, 927-935.

Björntorp, P., Holm, G., Rosmond, R., Folkow, B., 2000. Hypertension and the metabolic syndrome: closely related central origin?. Blood Press. 9, 71-82.

Brantley, P.J., Dietz, L.S., McKnight, G.T., Jones, G.N., Tulley, R., 1988. Convergence between the daily stress inventory and endocrine measures of stress. J. Consult. Clin. Psychol. 56, 549-551.

Brunner, E.J., Marmot, M.G., Nanchahal, K., Shipley, M.J., Stansfeld, S.A., Juneja, M., Alberti, K.G., 1997. Social inequality in coronary risk: central obesity and the metabolic syndrome. Evidence from the Whitehall II study. Diabetologia 40, 1341-1349.

Calogero, A.E., Gallucci, W.T., Chrousos, G.P., Gold, P.W., 1988. Interaction between GABAergic neurotransmission and rat hypothalamic corticotropin-releasing hormone secretion in vitro. Brain Res. 463, 28-36.

Cannon, W.B., 1939. The Wisdom of the Body. Norton, New York.

Chrousos, G.P., 1998. Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture. Ann. N.Y. Acad. Sci. 851, 311-335.

Chrousos, G.P., Gold, P.W., 1992. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. Jama 267, 1244-1252.

Chrousos, G.P., Gold, P.W., 1998. A healthy body in a healthy mind—and vice versa—the damaging power of uncontrollable stress. J. Clin. Endocrinol. Metab. 83, 1842-1845.

Clarkson, T.B., Kaplan, J.R., Adams, M.R., Manuck, S.B., 1987. Psychosocial influences on the pathogenesis of atherosclerosis among nonhuman primates. Circulation 76, I29-140.

Clarkson, T.B., Adams, M.R., Kaplan, J.R., Shively, C.A., 1989. Pathophysiology of coronary artery atherosclerosis: animal studies of gender differences. Cardiovasc. Clin. 19, 147-158.

Coderre, L., Vallega, G.A., Pilch, P.F., Chipkin, S.R., 1996. In vivo effects of dexamethasone and sucrose on glucose transport (GLUT-4) protein tissue distribution. Am. J. Physiol. 271, E643-E648.

Cummins, S.E., Gevirtz, R.N., 1993. The relationship between daily stress and urinary cortisol in a normal population: an emphasis on individual differences. Behav. Med. 19, 129-134.

Dallman, M., 1993. Stress update. Adaption of the hypothalamic-pituitary-adrenal axis to chronic stress. Trends Endocrinol. Metab. 4, 62-69.

Dallman, M.F., Strack, A.M., Akana, S.F., Bradbury, M.J., Hanson, E.S., Scribner, K.A., Smith, M., 1993. Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. Front. Neuroendocrinol. 14, 303-347.

Dallman, M.F., Akana, S.F., Levin, N., Walker, C.D., Bradbury, M.J., Suemaru, S., Scribner, K.S., 1994. Corticosteroids and the control of function in the hypothalamo-pituitary-adrenal (HPA) axis. Ann. N.Y. Acad. Sci. 746, 22-31 discussion 31-32, 64-67.

DeBold, C.R., Sheldon, W.R., DeCherney, G.S., Jackson, R.V., Alexander, A.N., Vale, W., Rivier, J., Orth, D.N., 1984. Arginine vasopressin potentiates adrenocorticotropin release induced by ovine corticotropin-releasing factor. J. Clin. Invest. 73, 533-538.

DeRijk, R.H., Schaaf, M., de Kloet, E.R., 2002. Glucocorticoid receptor variants: clinical implications. J. Steroid Biochem. Mol. Biol. 81, 103-122.

Dinan, T.G., 1996. Serotonin and the regulation of hypothalamic-pituitary-adrenal axis function. Life Sci. 58, 1683-1694.

Dunn, J.F., Nisula, B.C., Rodbard, D., 1981. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J. Clin. Endocrinol. Metab. 53, 58-68.

Fleury, I., Beaulieu, P., Primeau, M., Labuda, D., Sinnett, D., Krajinovic, M., 2003. Characterization of the BclI polymorphism in the glucocorticoid receptor gene. Clin. Chem. 49, 1528-1531.

Folkow, B., 1982. Physiological aspects of primary hypertension. Physiol. Rev. 62, 347-504.

Folkow, B., 1993. Physiological organization of neurohormonal responses to psychosocial stimuli: implications for health and disease. Ann. Behav. Med. 15, 236-244.

Folkow, B., 1997. Physiological aspects of the defence and defeat reactions. Acta Physiol. Scand. Suppl. 640, 34-37.

Garvey, W.T., Huecksteadt, T.P., Monzon, R., Marshall, S., 1989. Dexamethasone regulates the glucose transport system in primary cultured adipocytes: different mechanisms of insulin resistance after acute and chronic exposure. Endocrinology 124, 2063-2073.

Gosse, P., Dallocchio, M., 1993. Left ventricular hypertrophy: epidemiological prognosis and associated critical factors. Eur. Heart J. 14, 16-21.

Henry, J.P., 1992. Biological basis of the stress response. Integr. Physiol. Behav. Sci. 27, 66-83.

Henry, J.P., Grim, C.E., 1990. Psychosocial mechanisms of primary hypertension. J. Hypertens. 8, 783-793.

Herman, J.P., Cullinan, W.E., 1997. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci. 20, 78-84.

Holmäng, A., Björntorp, P., 1992. The effects of cortisol on insulin sensitivity in muscle. Acta Physiol. Scand. 144, 425-431.

Isomaa, B., Almgren, P., Tuomi, T., Forsen, B., Lahti, K., Nissen, M., Taskinen, M.R., Groop, L., 2001. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 24, 683-689.

Joels, M., de Kloet, E.R., 1994. Mineralocorticoid and glucocorticoid receptors in the brain. Implications for ion permeability and transmitter systems. Prog. Neurobiol. 43, 1-36.

Kaplan, J.R., Adams, M.R., Clarkson, T.B., Manuck, S.B., Shively, C.A., Williams, J.K., 1996. Psychosocial factors, sex differences, and atherosclerosis: lessons from animal models. Psychosom. Med. 58, 598-611.

Koutis, A.D., Lionis, C.D., Isacsson, A., Jakobsson, A., Fioretos, M., Lindholm, L.H., 1992. Characteristics of the metabolic syndrome X in a cardiovascular low risk population in Crete. Eur. Heart J. 13, 865-871.

Lambillotte, C., Gilon, P., Henquin, J.C., 1997. Direct glucocorticoid inhibition of insulin secretion. An in vitro study of dexamethasone effects in mouse islets. J. Clin. Invest. 99, 414-423.

Large, V., Hellström, L., Reynisdottir, S., Lönnqvist, F., Eriksson, P., Lannfelt, L., Arner, P., 1997. Human beta-2 adrenoceptor gene polymorphisms are highly frequent in obesity and associate with altered adipocyte beta-2 adrenoceptor function. J. Clin. Invest. 100, 3005-3013.

Lazarus, R.S., 1993. Coping theory and research: past, present, and future. Psychosom. Med. 55, 234-247.

Lee, Z.S., Critchley, J.A., Chan, J.C., Anderson, P.J., Thomas, G.N., Ko, G.T., Young, R.P., Chan, T.Y., Cockram, C.S., Tomlinson, B., 2000. Obesity is the key determinant of cardiovascular risk factors in the Hong Kong Chinese population: cross-sectional clinic-based study. Hong Kong Med. J. 6, 13-23.

Marmot, M.G., McDowall, M.E., 1986. Mortality decline and widening social inequalities. Lancet 2, 274-276.

Mason, J.W., 1971. A re-evaluation of the concept of non-specificity in stress theory. J Psychiatr. Res. 8, 323-333.

Mason, J.W., 1975. A historical view of the stress field. J. Hum. Stress 1, 22-36.

McEwen, B.S., 1998. Protective and damaging effects of stress mediators. N. Engl. J. Med. 338, 171-179.

McEwen, B.S., Stellar, E., 1993. Stress and the individual. Mechanisms leading to disease. Arch. Intern. Med. 153, 2093-2101.

Meigs, J.B., Wilson, P.W., Nathan, D.M., D'Agostino Sr.., R.B., Williams, K., Haffner, S.M., 2003. Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. Diabetes 52, 2160-2167.

Montkowski, A., Barden, N., Wotjak, C., Stec, I., Ganster, J., Meaney, M., Engelmann, M., Reul, J.M., Landgraf, R., Holsboer, F., 1995. Long-term antidepressant treatment reduces behavioural deficits in transgenic mice with impaired glucocorticoid receptor function. J. Neuroendocrinol. 7, 841-845.

Mores, N., Martire, M., Pistritto, G., Cardillo, C., Folli, G., 1990. A discrepancy between platelet alpha 2-receptor density and functional circulatory changes in hypertensives. J. Cardiovasc. Pharmacol. 16, 411-416.

Must, A., Spadano, J., Coakley, E.H., Field, A.E., Colditz, G., Dietz, W.H., 1999. The disease burden associated with overweight and obesity. Jama 282, 1523-1529.

Ottosson, M., Vikman-Adolfsson, K., Enerbäck, S., Olivecrona, G., Björntorp, P., 1994. The effects of cortisol on the regulation of lipoprotein lipase activity in human adipose tissue. J. Clin. Endocrinol. Metab. 79, 820-825.

Pagano, G., Cavallo-Perin, P., Cassader, M., Bruno, A., Ozzello, A., Masciola, P., Dall'omo, A.M., Imbimbo, B., 1983. An in vivo and in vitro study of the mechanism of prednisone-induced insulin resistance in healthy subjects. J. Clin. Invest. 72, 1814-1820.

Pepin, M.C., Pothier, F., Barden, N., 1992. Impaired type II glucocorticoid-receptor function in mice bearing antisense RNA transgene. Nature 355, 725-728.

Ragland, D.R., Brand, R.J., 1988. Type A behavior and mortality from coronary heart disease. N. Engl. J. Med. 318, 65-69.

Reaven, G.M., 1988. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37, 1595-1607.

Rebuffe-Scrive, M., Lundholm, K., Björntorp, P., 1985. Glucocorticoid hormone binding to human adipose tissue. Eur. J. Clin. Invest. 15, 267-271.

Rebuffe-Scrive, M., Brönnegård, M., Nilsson, A., Eldh, J., Gustafsson, J.A., Björntorp, P., 1990. Steroid hormone receptors in human adipose tissues. J. Clin. Endocrinol. Metab. 71, 1215-1219.

Reichlin, S., 1993. Neuroendocrine-immune interactions. N. Engl. J. Med. 329, 1246-1253.

Reihsaus, E., Innis, M., MacIntyre, N., Liggett, S.B., 1993. Mutations in the gene encoding for the beta 2-adrenergic receptor in normal and asthmatic subjects. Am. J. Respir. Cell Mol. Biol. 8, 334-339.

Reynolds, R.M., Chapman, K.E., Seckl, J.R., Walker, B.R., McKeigue, P.M., Lithell, H.O., 2002. Skeletal muscle glucocorticoid receptor density and insulin resistance. JAMA 287, 2505-2506.

Rosmond, R., 2001. Visceral obesity and the metabolic syndrome, in: Björntorp, P. (Ed.), International Textbook of Obesity. Wiley, Chichester, pp. 339-350.

Rosmond, R., 2002. The glucocorticoid receptor gene and its association to metabolic syndrome. Obes. Res. 10, 1078-1086.

Rosmond, R., 2003. Association studies of genetic polymorphisms in central obesity: a critical review. Int. J. Obes. Relat. Metab. Disord. 27, 1141-1151.

Rosmond, R., Björntorp, P., 2000. Occupational status, cortisol secretory pattern, and visceral obesity in middle-aged men. Obes. Res. 8, 445-450.

Rosmond, R., Chagnon, Y.C., Holm, G., Chagnon, M., Perusse, L., Lindell, K., Carlsson, B., Bouchard, C., Björntorp, P., 2000. A glucocorticoid receptor gene marker is associated with abdominal obesity, leptin, and dysregulation of the hypothalamic-pituitary-adrenal axis. Obes. Res. 8, 211-218.

Rosmond, R., Chagnon, M., Bouchard, C., Björntorp, P., 2001. G-308A polymorphism of the tumor necrosis factor alpha gene promoter and salivary cortisol secretion. J. Clin. Endocrinol. Metab. 86, 2178-2180.

Rosmond, R., Bouchard, C., Björntorp, P., 2002. Allelic variants in the GABA(A)alpha6 receptor subunit gene (GABRA6) is associated with abdominal obesity and cortisol secretion. Int. J. Obes. Relat. Metab. Disord. 26, 938-941.

Rosmond, R., Bouchard, C., Björntorp, P., 2002. A C-1291G polymorphism in the alpha2A-adrenergic receptor gene (ADRA2A) promoter is associated with cortisol escape from dexamethasone and elevated glucose levels. J. Intern. Med. 251, 252-257.

Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1986. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr. Rev. 7, 284-301.

Selye, H., 1956. The Stress of Life. McGraw Hill, New York.

Selye, H., 1982. Stress: eustress, distress, and human perspectives, in: Day, S.B. (Ed.), Life Stress. Van Nostrand Reinhold, New York, pp. 3-13.

Shively, C.A., Kaplan, J.R., Clarkson, T.B., 1990. Carotid artery atherosclerosis in cholesterol-fed female cynomolgus monkeys. Effects of oral contraceptive treatment, social factors, and regional adiposity. Arteriosclerosis 10, 358-366.

Skinner, J.E., 1985. Psychosocial stress and sudden cardiac death: brain mechanisms, in: Beamish, R.E., Singal, P.K., Dhalla, N.S. (Eds.), Stress and Heart Disease. Martinus Nijhoff, Boston, pp. 44-59.

Sterling, P., Eyer, J., 1988. Allostasis: a new paradigm to explain arousal pathology, in: Fisher, S., Reason, J. (Eds.), Handbook of Life Stress, Cognition and Health. Wiley, New York, pp. 629-649.

Taylor, A.L., Fishman, L.M., 1988. Corticotropin-releasing hormone. N. Engl. J. Med. 319, 213-222.

Trevisan, M., Liu, J., Bahsas, F.B., Menotti, A., 1998. Syndrome X and mortality: a population-based study. Risk Factor and Life Expectancy Research Group. Am. J. Epidemiol. 148, 958-966.

Ukkola, O., Rosmond, R., Tremblay, A., Bouchard, C., 2001. Glucocorticoid receptor Bcl I variant is associated with an increased atherogenic profile in response to long-term overfeeding. Atherosclerosis 157, 221-224.

Vanhala, M.J., Kumpusalo, E.A., Pitkajarvi, T.K., Takala, J.K., 1997. Metabolic syndrome' in a middle-aged Finnish population. J. Cardiovasc. Risk 4, 291-295.

Währborg, P., 1998. Mental stress and ischaemic heart disease: an underestimated connection. Eur. Heart J. 19, O20-O23.

Wajngot, A., Khan, A., Giacca, A., Vranic, M., Efendic, S., 1990. Dexamethasone increases glucose cycling, but not glucose production, in healthy subjects. Am. J. Physiol. 259, E626-E632.

Wannamethee, S.G., Shaper, A.G., Durrington, P.N., Perry, I.J., 1998. Hypertension, serum insulin, obesity and the metabolic syndrome. J. Hum. Hypertens. 12, 735-741.

Wilson, A.G., di Giovine, F.S., Blakemore, A.I., Duff, G.W., 1992. Single base polymorphism in the human tumour necrosis factor alpha (TNF alpha) gene detectable by NcoI restriction of PCR product. Hum. Mol. Genet. 1, 353.

Wilson, A.G., Symons, J.A., McDowell, T.L., McDevitt, H.O., Duff, G.W., 1997. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proc. Natl Acad. Sci. USA 94, 3195-3199.

WHO, 2000. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Technical Report Series 894:i-xii, pp. 1-253.

Yarbrough, D.E., Barrett-Connor, E., Kritz-Silverstein, D., Wingard, D.L., 1998. Birth weight, adult weight, and girth as predictors of the metabolic syndrome in postmenopausal women: the Rancho Bernardo Study. Diabetes Care 21, 1652-1658.

York, D.A., 1996. Lessons from animal models of obesity. Endocrinol. Metab. Clin. North Am. 25, 781-800.