Part V

Complications

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Visceral Obesity and the Metabolic Syndrome

Roland Rosmond

Sahlgrenska University Hospital, Göteborg, Sweden

INTRODUCTION—EPIDEMIOLOGY

The association between obesity and type 2 (non-insulin-dependent) diabetes mellitus has been recognized for several decades. It has now been shown that obesity is also associated with cardiovascular disease (CVD) and stroke. Population-based follow-up studies have revealed this concealed link, bringing the importance of obesity as an independent risk factor for cardiovascular morbidity and mortality to the forefront. However, at first, it was assumed that only severe obesity was as powerful a risk indicator of CVD and stroke as other, established risk factors such as hypercholesterolaemia and high blood pressure.

Retrospectively, it is now possible to identify why these studies failed to highlight the impact of excess body fat on cardiovascular morbidity. First, in analysing epidemiological data, it is common to adjust for the effect of some variables believed to distort the results, and in the case of obesity, adjustments were made for comorbidities such as dyslipidaemia, hypertension, insulin resistance and impaired glucose tolerance. However, these adjustments are biologically and clinically implausible, since obesity without such comorbidities is a rare condition. Furthermore, severe non-orthogonality is introduced in the statistical analyses since these comorbidities are highly correlated. Another problem with these early studies was that obesity, defined as increased body fat mass, was treated as one homogeneous entity. Human obesity has repeatedly been subjected to subdivisions with the clinical intuition that this is not one single disease, but rather a symptom of several underlying conditions, to some extent similar to diseases such as anaemia–polyglobulinaemia, where red blood cells vary in amount and quality for a number of underlying reasons.

Human obesity is characterized by a wide variation in the distribution of excess body fat, and the distribution of fat affects the risks associated with obesity as well as the kinds of comorbidities that result. In the 1920s the idea emerged, under Kretschmer's influence (1), that the pychnic type of body build was associated with abdominal obesity, gout, apoplexia and impaired glucose tolerance. Vague extended these observations further and labelled obesity types android (male-type) and gynoid (female-type), and noted that, although gender-specific in general, women might have android obesity and vice versa (2). Nevertheless, the android type of obesity carries a greater risk for disease in both men and women.

In addition to the pioneering attempts by Kretschmer and Vague to categorize obesity, recent developments have confirmed the higher prevalence of dyslipidaemia, insulin resistance and hypertension in abdominal, central obesity in comparison with the more peripherally distributed, gluteofemoral obesity (3,4), The techniques for the assessment of adipose tissue in these studies were

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simpler than those employed by Vague (2), and included the ratio of waist and hip circumferences (WHR). Central obesity is thus more strongly associated with comorbidities in various systems than is peripheral obesity. This is particularly evident when intra-abdominal, visceral fat depots are enlarged (5,6).

The results of prospective epidemiological studies presented a major breakthrough in the significance of this type of categorization of obesity. These studies showed that WHR contributes independently to the risk of type 2 diabetes, CVD and stroke in both men and women, and is as powerful a predictor as other established risk factors for these diseases. Moreover, these studies showed that general obesity, measured as body mass index (BMI, weight (kg)/height^2 [m^2]), was not necessarily a part of this health hazard (7,8).

Subsequent studies have indicated other health consequences of central obesity such as cancer of the endometrium (9), breast (10) and ovaries (9) in women, and the prostate in men (11). The respiratory function when measured in obese subjects reveals many abnormalities, and one of the most extreme is the Pickwickian hypoventilation syndrome. Obstructive sleep apnoea is also common in obesity, and about 50% of subjects with this disorder are moderately to severely abdominally obese (12). Cholelithiasis and obesity has been documented in several studies (11), and hepatic steatosis occurs in about 68–94% of obese individuals (13).

PATHOGENETIC ASPECTS

These statistical observations imply a major, fundamental, systematic pathogenetic background to abdominal, visceral fat accumulation and its associated multiple comorbidities. From a clinical point of view, there is a perceptible resemblance between this condition and that of Cushing's syndrome. In fact, subjects with abdominal, visceral obesity share many of the metabolic, hormonal, circulatory and behavioural findings observed in Cushing's syndrome. It may therefore be suspected that the regulation of cortisol secretion is involved in the syndrome of visceral obesity (5,14).

Studies driven by this hypothesis suggested that urinary cortisol output was elevated with elevated WHR (15). Although statistically significant, the original findings were strongly influenced by a few extreme observations. It is also clear that the cortisol output is frequently normal or even low in subjects with elevated WHR (Figure 1 in reference 15). Results of other studies indicated that when the hypothalamic-pituitary-adrenal (HPA) axis, regulating cortisol secretion, was stimulated at the levels of the adrenals with adrenocorticotrophic hormone (ACTH), the pituitary with corticotrophin-releasing hormone (CRH) and the hypothalamic centres by laboratory stress, the total urinary output of cortisol appeared to be elevated in subjects with high WHR (15,16). However, the challenges at the different levels of the HPA axis were performed with maximal doses of ACTH and CRH. The use of such doses provides information about the responsiveness rather than sensitivity of the regulatory system. Maximal stimulation rarely, if ever, occurs under ordinary, everyday life conditions, and these results therefore had minor significance for the issue addressed.

METHODOLOGICAL DEVELOPMENTS

The idea that frequent or persistent challenges of the 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 homeostatic processes. Although biologically plausible, this complex hypothesis has been difficult to study in humans (17), presumably as a result of several inherent problems.

The pattern of ACTH and cortisol variations shows an early morning peak, declining levels during the daytime and minimal secretory activity in the evening. This secretory pattern is brought about by the nervous system. There is, however, no sharp distinction between the endocrine and nervous systems, and in the hypothalamus and the pituitary there is a close connection between these two systems that integrates the two into one control unit. The CRH-secreting neurons, located within the paraventricular nuclei (PVN) (18), receive afferent regulatory signals from different parts of the brain. Stimulatory inputs arise from the suprachiasmatic nucleus (the regulator of circadian rhythms), the amygdala and the raphe nuclei (19,20), while inhibitory inputs on CRH secretion arise in the hippocampus and in the locus coeruleus. The CRH

neurons are excitatory, influenced by cholinergic and serotoninergic central pathways (21). Inhibitory effects are exerted by γ-aminobutyric acid (GABA) (20). Catecholamines can exert both inhibitory and excitatory effects (22). Furthermore, stimulation of hypothalamic opioid peptide (POMC-producing) neurons will inhibit the release of CRH from the PVN (23).

In summary, the central nervous system provides inputs in terms of registrations by the senses, modified by experience and coping ability, and the integrated resulting signals transferred to the hypothalamus. These afferent signals are balanced by endocrine feedback regulation, mediated via glucocorticoid receptors (GR) in the hippocampus and the amygdala (24–26). Feedback information allows the HPA axis to adjust appropriately the cortisol secretion from the adrenals.

When measurements are performed aimed at elucidating the natural, spontaneous, everyday activity of the HPA axis, several prerequisites have to be considered. The regulation of the HPA axis is greatly affected by environmental disturbances. For instance, the artificial milieu of a laboratory or a hospital may distort normal activity, and even minor venepuncture per se can significantly increase cortisol concentration in serum. Urinary cortisol measurements offer a tool to circumvent this source of bias. However, urinary measurements do not reveal the secretory pattern of cortisol, which is, as will be seen in the following, vital information. Moreover, the technique is usually restricted for practical reasons to inpatients.

The assessment of cortisol in saliva provides several advantages over blood cortisol measurements, as the collection procedure is non-invasive and stress free, making it ideal for use in psychoneuroendocrinological research. Since salivary cortisol sampling is laboratory independent, it can be applied under a variety of field settings. It is well documented that salivary cortisol provides the clinician with a reliable tool for examination of pathological conditions characterized by abnormal cortisol secretion (27–30). Cortisol is lipid-soluble which enables the molecule to diffuse rapidly to the acinar cells of the salivary glands via the bloodstream, and then pass easily through these cells into saliva. Neither maximal stimulation of saliva flow (28) nor minimal secretion of saliva following medication with anticholinergic side effects influences the concentration of cortisol in saliva (27). Moreover, cortisol in saliva represents the unbound ('free') hormone fraction, and reflects accurately the free fraction of cortisol in plasma, despite the conversion of cortisol to cortisone in saliva by 11β-hydroxysteroid dehydrogenase (31).

To obtain a biochemical evaluation of the HPA axis activity and regulation that is as complete as possible several details are essential. A normal diurnal variation is a pattern in which cortisol levels are high and varying in the morning and from 1600 hours to midnight less than 75% of the morning values. This must be recorded together with the total cortisol levels. Since the HPA axis is subject to periodic or cyclic changes (19), the measurement of cortisol levels at various times of the day to determine the presence or absence of a circadian rhythm is crucial. Furthermore, the response to external stimuli is informative, and the physiological input by food intake can be measured, if the stimulus is standardized. Various centrally occurring challenges of the HPA axis, in terms of stress, are of fundamental importance, and as stressors are perceived differently, individual coping ability has to be taken into account. This is accomplished by reports by the proband of perceived stress.

In addition to these measurements of basal and stimulated HPA axis activity, the response to exogenous glucocorticoids is required to detect abnormal feedback regulation of ACTH and cortisol secretion (32). Conventionally dexamethasone is given in a dose of 1 mg, which is usually followed by a complete inhibition of ACTH and cortisol secretion, except in subjects with Cushing's syndrome. Preliminary examinations showed that utilizing a low dose (0.5 mg $\times$ 1) of dexamethasone (33) reveals mild abnormalities in the ability of the central glucorticoid receptor (GR) to control the HPA axis by feedback inhibition that cannot be discovered with the conventional dose of 1 mg (15).

In summary, these different characteristics of the HPA axis activity and regulation were measured by a series of saliva sampling during the day, in which cortisol levels were measured. A sample was obtained in the morning (0800–0900 hours), then at 1145 hours, and 30, 45 and 60 minutes after a standardized lunch at 1200 hours, 1700 hours, and finally just before bedtime. Within these periods, relatively small changes in unstimulated cortisol values occur and therefore a satisfactory estimation of the circadian rhythm can be acquired (34). The circadian rhythm of cortisol secretion was estimated

as the variability of cortisol secretion. By addition of all measured values, a measurement of total cortisol secretion was obtained. The response to lunch was calculated as the peak of cortisol after lunch. Stress-related cortisol secretion was calculated as the response of cortisol to simultaneously reported perceived stress. Finally, the low dose (0.5 mg × 1) dexamethasone suppression test was performed similarly at home.

METHODOLOGICAL COMPARISONS

The concentration of cortisol in saliva, although approximately 30–50% lower (34), correlates closely with the concentration of free cortisol in serum ($r \approx 0.90$). Consequently, salivary cortisol measurements are an excellent index of the total, free cortisol concentration in serum as well as in urine in both normal and pathological conditions (27–30).

Cortisol has effects at nearly all levels in the human body, including an important role in lipid and glucose metabolism. Cortisol also inhibits most inflammatory processes (35), increases the left ventricular work index (36), and increases glomerular filtration rate, renal blood flow and potassium and acid excretion (37,38).

Centralization of body fat is most likely an effect of cortisol, as clearly seen in Cushing's syndrome, exhibited as severe truncal obesity. After successful therapy, the somatic features of Cushing's syndrome disappear (39). This provides evidence that cortisol may have a most potent stimulatory effect on central, visceral fat accumulation. Further evidence suggests that cortisol, in the presence of insulin, activates the main gateway for lipid accumulation in adipocytes, the lipoprotein lipase (LPL) enzyme, by actions on the processes of transcription and post-translation (40,41). Moreover, under these conditions the activity of the lipid mobilization system is low (41). These metabolic processes are mediated throughout the GR in adipose tissue. High activity in the lipid accumulating pathway together with low activity of lipid mobilization, exerted by cortisol, will be most pronounced is visceral fat depots due to the high density of GR (42). In light of this clinical and interventional evidence, strengthened by experimental studies, it is thus obvious that cortisol plays a major role as an aetiological factor in visceral fat accumulation.

With this background, it becomes relevant to determine to what extent salivary cortisol levels correlate to centrally localized body fat. Furthermore, it has been assumed that measurements of body fat centralization reflect a persistent, inappropriate cortisol secretion and related endocrine phenomena (43). In support of this assumption, anthropometric measurements were also correlated to the salivary cortisol assessments.

The presence of a normal circadian rhythm (variability) and feedback regulation (dexamethasone) of the HPA axis, along with an adequate response to stimuli (lunch), shows significant correlations with waist circumference (W) and abdominal sagittal diameter (D) (Table 23.1). The same results are also seen with an abnormal HPA axis, characterized by low variability and poor feedback regulation. Total cortisol secretion, however, showed no statistically significant relationship to the measurements of central obesity (W and D). In fact, total cortisol secretion even showed a negative association with WHR.

In conclusion, these findings suggest that the relationship between cortisol and central obesity can be entirely unveiled provided that the HPA axis is subjected to external stimulus or challenges, and that the total cortisol secretion per se is inappropriate for such purposes.

The BMI, an estimation of the total body fat mass regardless of regional distribution, showed several significant relationships to the functional status of the HPA axis. This indicates an association between general obesity, measured as BMI, and the HPA axis. This is further supported by means of structural equation modelling (path analysis) where a direct link between the HPA axis function and BMI was found (44). Given this information, together with previous studies (45) suggesting leptin resistance in obesity, we performed analyses of leptin with similar results—namely, an increase in leptin concentration is associated with elevated BMI (46). In addition, recent studies imply that cortisol may give rise to such a leptin resistance (47–49). There is thus a prospect that leptin concentrations are influenced by the HPA axis, and that increased total cortisol secretion with a normal axis, and evoked cortisol secretion by various stimulis with an abnormal axis (Table 23.1), may actually induce obesity. This would explain the well-known clinical observation that hypercortisolism, as in Cushing's syndrome or as an effect of corticosteroid

Table 23.1 Correlations between the function of the hypothalamic-pituitary-adrenal (HPA) axis and anthropometric measurements in middle-aged men

	BMI	WHR	W	D
Normal HPA axis				
Total cortisol level (nmol/L)	− 0.13 ($P = 0.035$)	− 0.08 ($P = 0.196$)	− 0.09 ($P = 0.153$)	− 0.11 ($P = 0.068$)
Cortisol after lunch (nmol/L)	0.16 ($P = 0.005$)	0.03 ($P > 0.200$)	0.22 ($P < 0.001$)	0.18 ($P = 0.001$)
Stress-related cortisol	0.01 ($P > 0.200$)	0.01 ($P > 0.200$)	− 0.01 ($P > 0.200$)	0.17 ($P = 0.002$)
Abnormal HPA axis				
Total cortisol level (nmol/L)	0.01 ($P > 0.200$)	− 0.10 ($P = 0.001$)	− 0.05 ($P = 0.087$)	0.04 ($P = 0.190$)
Cortisol after lunch (nmol/L)	0.14 ($P < 0.001$)	0.07 ($P = 0.003$)	0.10 ($P < 0.001$)	0.15 ($P < 0.001$)
Stress-related cortisol	0.35 ($P < 0.001$)	0.41 ($P < 0.001$)	0.37 ($P < 0.001$)	0.44 ($P < 0.001$)

BMI, body mass index (kg/m^2); WHR, waist-to-hip circumference ratio; W, waist circumference (cm); D, abdominal sagittal diameter (cm). Modified from references 67–69.

therapy, is followed by obesity, whereas deficient secretion of cortisol, as in Addison's disease, is followed by anorexia. Moreover, in experimental models, obesity is frequently associated with an elevated adrenal secretion of cortisol, and upon adrenalectomy weight loss is successfully achieved (50).

In previous studies (7,8), the WHR was presumed to reflect an abnormal cortisol secretion, and as seen in Table 23.1, this assumption appears to be valid when the HPA axis is provoked by physiological challenge (lunch) or perceived stress. However, other endocrine perturbations are also involved in the syndrome of visceral obesity, as will be discussed later.

These results may be summarized as follows. Measurements of regional fat distribution by WHR, W or D, when elevated, are sufficient and useful indicators of adaptations of HPA axis activity, particularly when the axis is provoked by external stimuli. The accompanying neuroendocrine changes, however, do not necessarily comprise an elevated total cortisol secretion. Furthermore, the results support the anthropometric measurements (WHR, W, and D) as useful tools for large-scale population and epidemiological studies when HPA axis activity measurements in a clinical setting are not feasible.

In conclusion, the WHR may thus be substituted theoretically by HPA axis abnormalities when interpreting studies where the WHR displays a powerful independent risk factor for mortality and morbidity. In addition, factors related to the WHR such as low socioeconomic status (51,52), alcohol and smoking (53,54), and psychiatric ill health (55–57), may accordingly be substituted by HPA axis perturbations, known to arise after frequently repeated or chronic stress (25).

SUBGROUPING OF VISCERAL OBESITY WITH THE METABOLIC SYNDROME

Visceral obesity is associated with other endocrine abnormalities than that of cortisol. Indeed, visceral obese individuals with the metabolic syndrome may have all the hormonal abnormalities of the elderly, suggesting that this condition may be a sign of premature ageing (58). The most common deficiencies are those of growth hormone (GH) and sex steroids (59). Whereas men have low testosterone levels (60), women have irregular menstrual cycles (61). Functionally, the growth axis and the reproductive axis are influenced at many levels by the HPA axis. Prolonged activation of the HPA axis thus leads to suppression of GH secretion as well as inhibition of sex steroids (23,62).

These endocrine abnormalities have a profound effect on peripheral tissues. While cortisol promotes accumulation of visceral fat and insulin resistance in muscle tissue, the GH and sex steroids, often in concert, do the opposite (42). Low GH and sex steroid secretions will thereby multiply the pathogenetic effects of cortisol. In fact, there is evidence that low concentrations of GH and sex steroids without HPA axis perturbations may cause such effects. As a result, visceral obesity with the metabolic syndrome may originate on the basis of the following endocrine subgroups: one characterized by HPA axis perturbation, the other character-

ized by low secretion of GH and sex steroid, and finally, a combination of both these events.

This issue was addressed in a recently performed cohort study of middle-aged men (44). Subgroups were constructed based on the current clinical definition of low testosterone and insulin-like growth factor I (IGF-I), a mediator of the major actions of GH (63), and the dexamethasone suppression test as a measurement of the feedback regulation system. In the total cohort of men ($N = 284$), assessments of visceral obesity correlated strongly and consistently with all metabolic parameters except total and low density lipoprotein cholesterol. Furthermore, visceral obesity was found to be associated with elevated blood pressure and heart rate. Identical findings appeared within the subgroup characterized by HPA axis perturbation, defined as a blunted response to dexamethasone. This was also the case in the subgroup characterized by low secretion of testosterone and IGF-I. These results support the concept of endocrine subgrouping of visceral obesity with the metabolic syndrome.

In addition to these analyses, structural equation modelling (path analysis) was performed to examine potential causal models between the endocrine (testosterone and IGF-I), the anthropometric (WHR and D), and selected metabolic measurements (insulin and triglycerides). The results obtained are summarized in Figure 23.1. A blunted response to dexamethasone, that is, a HPA axis characterized by poor feedback regulation, was directly associated with low concentrations of testosterone and IGF-I as well as elevated levels of insulin. Low testosterone and IGF-I in turn was linked to increased WHR and D, and these anthropometric measurements were associated with hyperinsulinaemia, which was related to elevated levels of triglycerides. This chain of events suggests that HPA axis perturbations contribute to the outgrowth of central obesity and insulin resistance. The latter is also further influenced by central obesity measured as WHR or D. Figure 23.1 illustrates the impact of low testosterone and IGF-I on centralization of body fat stores. Thus, input into this chain of events, resulting in metabolic aberrations, may occur at different levels: the HPA axis, isolated testosterone and IGF-I deficiency, or by visceral obesity itself. This interpretation is in excellent agreement with the endocrine subgrouping of the metabolic syndrome as discussed above.

In summary, these findings suggest the possibility

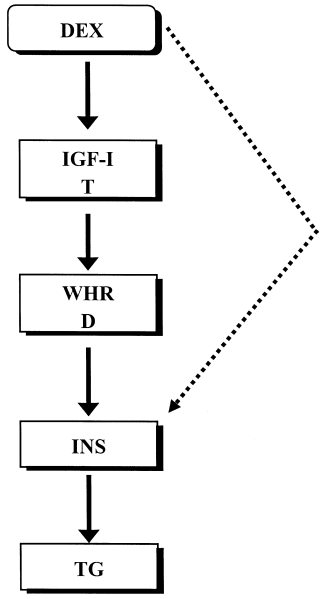

Figure 23.1 Summary of path analyses. DEX, blunted dexamethasone (0.5 mg × 1) suppression of cortisol secretion (nmol/L); IGF-I, insulin-like growth factor I (μg/L); T, testosterone (nmol/L); WHR, waist-to-hip circumference ratio; D, abdominal sagittal diameter (cm); INS, insulin (mU/L); TG, triglycerides (mol/L). Modified from reference 44

that visceral obesity with the metabolic syndrome may originate from other sources than primary perturbations of the HPA axis. For instance, primary deficiency of GH or testosterone might result in the metabolic syndrome; after adequate hormonal replacement therapy, the anthropometric, metabolic and circulatory abnormalities of the metabolic syndrome are successfully restored (64–66). This suggests a causal relationship between such endocrine deficiencies and visceral obesity with the metabolic syndrome.

SUBGROUPING OF THE HPA AXIS PERTURBATIONS

Throughout recently performed studies (67–70), we have been able to single out subgroups of the functional status of the HPA axis within a general population of non-cushingoid middle-aged men. The first group was characterized by a high morning cortisol peak, a normal circadian rhythm (variability) and feedback regulation (dexamethasone) along

Table 23.2 Stages of the hypothalamic-pituitary-adrenal axis status and feedback regulation with peripheral consequences

Stages	Endocrine Status	Feedback regulation	Peripheral consequences
I. Steady-state	Normal	Normal	None
II. Acute stress	High cortisol	Normal	↑ Accumulation of visceral fat ↑ Glucose, fatty acids and triglycerides
III. Repeated stress	High → Low cortisol Normal → Low GH and sex steroids	Normal → Blunted	Visceral obesity Metabolic syndrome Elevated BP
IV. Chronic stress	Low cortisol Low GH and sex steroids	Blunted	Visceral obesity Metabolic syndrome Elevated BP and HR

GH, growth hormone; BP, blood pressure; HR, heart rate.

with a brisk cortisol response to lunch. Such men are in general lean, measured as BMI and WHR, with higher values of IGF-I than average, and low total and low density lipoprotein (LDL) cholesterol as well as blood pressure.

The other group identified was characterized by the absence of a morning cortisol peak and circadian rhythm, a blunted suppression of cortisol by overnight low dose dexamethasone and a poor lunch-induced cortisol response. Such men suffer from obesity with a predominance of centrally located body fat, low testosterone and IGF-I concentrations, high glucose, insulin, triglycerides, total and LDL cholesterol, blood pressures and heart rate, while high density lipoprotein cholesterol is low. These relationships are all highly statistically significant (P values < 0.001), and consistent with the current opinion about the health consequences of an abnormally functioning HPA axis (17). Such men thus have visceral obesity with metabolic syndrome, including hypercholesterolaemia and hypertension. This is in contrast to men with a normal HPA axis function, and further emphasizes the importance of the HPA axis for human health (17,67–70).

In an attempt to highlight the importance of the HPA axis in human health, we performed multidimensional scaling analyses of the anthropometric, metabolic and circulatory risk factors for CVD, type 2 diabetes and stroke (70). Under the influence of an abnormal HPA axis, as described above, all these risk factors congregate into one distinct, strongly intercorrelated cluster (70). This indicates an overriding direct control of the conventional risk factors by such HPA axis perturbations.

STAGES OF THE HPA AXIS FUNCTIONAL STATUS

The above subgroups of the functional status of the HPA axis represent extremes in terms of the resiliency of the HPA axis. Although strongly genetically determined (71), environmental and social factors also affect the circadian rhythm of the HPA axis (72). The question arises whether there are time- and stress-related changes in patterns of HPA axis activity and regulation, and if it is possible to tentatively define stages of such HPA axis affliction. A *first stage* then would be a normal function of the HPA axis, defined as a normal circadian rhythm with high morning and low afternoon–evening cortisol levels, and normal feedback control of GRs. Total cortisol output is regulated within the normal range and this is associated with optimal health. A *second stage* is seen upon acute stress where central regulation of HPA axis rhythm is maintained as well as the feedback control. The growth and reproductive axes are not affected. Cortisol secretion will, however, be elevated with peripheral consequences if prolonged. A *third stage* appears when frequently repeated stress challenges the central regulation of HPA axis function. The GRs will be downregulated (26,73), resulting in a poor feedback control of ACTH and cortisol secretion. The elevated cortisol secretion will then eventually become low. This prolonged activation of the HPA axis will also suppress the GH and sex steroid secretions (23). The peripheral consequences will now be a full-blown metabolic syndrome. A *fourth and final stage* is that of chronic stress, with a 'burn-out' of central regulatory systems (25,26,74), resulting in a net decrease of

cortisol output and inhibition of other endocrine axes resulting in a metabolic syndrome. These stages are summarized in Table 23.2.

GENETIC ASPECTS

As discussed above, the glucocorticoid feedback effects exerted on the pituitary and the hippocampus become blunted during stages III and IV. The feedback is initiated by binding of steroid to regulatory gene elements (75), and the feedback suppression is mediated by glucocorticoid receptors (GR) in the hippocampus (25,26). Studies *in vivo*, and *in vitro*, in cells from chronically stressed rats, have shown that the sensitivity of the HPA axis to inhibition by cortisol is impaired (76,77). When the HPA axis is subjected to prolonged elevation of cortisol levels as in chronic stress, the GRs gradually loses their function, ending up in a presumably irreversible neurodegenerative condition (74). Such hippocampal damage has been observed in individuals with Cushing's syndrome (78), a condition also characterized by hypercortisolism.

A dose–response study of inhibition by dexamethasone administration has shown that feedback regulation in subjects with visceral obesity is diminished (33), in parallel with a blunted function of GR in adipose tissue (Ottosson *et al*., unpublished data). The latter study indicates the possibilities of both a decreased responsiveness and sensitivity of the GRs. Consequently, the GR gene (GRL), located in chromosome 5 and consisting of 10 exons with a minimum size of 80 kilobases (kb) (79), has been partially sequenced. However, no abnormalities in the DNA-binding (exon 2) or steroid binding (exon 9) domains of the GRL have been revealed (unpublished data). Nevertheless, the recent discovery that a *Bcl*I GRL polymorphism is associated with elevated cortisol concentrations in response to metabolic stress has raised the possibility that mutations may decrease the sensitivity to cortisol feedback (46). With the restriction enzyme *Bcl*I two alleles with fragment lengths of 4.5 and 2.3 kb are discoverable. The 4.5 kb allele is known to be associated with visceral obesity and insulin resistance (80,81). Furthermore, individuals carrying the 4.5 kb allele have higher leptin values (46). While the *Bcl*I restriction enzyme cleaves the GRL in the first intron the functional role of the polymorphism, if any, is uncertain. However, a polymorphism in an intron may interfere with splicing of primary mRNA or serves as an index for functionally important polymorphisms in neighbouring gene domains, including the promotor region. With the restriction enzyme *TthIII*1, a variant of the 5′-flanking region of the GRL is discoverable as two alleles with fragment lengths of 3.4 and 3.8 kb (82). Individuals carrying the 3.8 kb allele have higher total and evening cortisol levels with trends for elevated levels over the day (82). This polymorphism is localized in the 5′-flanking region of the GRL gene locus, probably in the promotor region of the gene, and may therefore be involved in the regulation of GR density.

HYPERTENSION

Hypertension is closely related to the metabolic syndrome (43,83), and since hypertension is statistically associated with insulin (84), several authors have postulated that hyperinsulinaemia is related to blood pressure independently of body fat mass (85–87). However, hyperinsulinaemia is not found in all obese subjects and not all hypertensive subjects are obese (88). Recent studies have revealed that visceral obesity and HPA axis perturbations are independently related to blood pressure, and that insulin and insulin resistance may account for only a part of this association (89). This suggests that hypertension with accompanying, observed increases in heart rate may have a central origin. Although the pathophysiology of essential hypertension is still unclear, it is generally accepted that activation of the central sympathetic nervous system can increase blood pressure (90,91). We have suggested that the simultaneous activation of the sympathetic nervous system and the HPA axis might be mediated via a common arousal of hypothalamic centres (69). Such a hypothalamic arousal syndrome may provide an excitatory influence on both the sympathetic nervous system, resulting in hypertension, and the HPA axis, resulting in visceral obesity with the metabolic syndrome. This would explain the statistical relationship between hypertension and insulin resistance as well as the kinds of metabolic abnormalities that result.

ENVIRONMENTAL FACTORS INFLUENCING THE HPA AXIS

This overview has explored the pathophysiological consequences of an evoked, excessive perturbation of one of the principal axes of neuroendocrine response in the human body. In the following section, the environmental factors that influence the HPA axis will be reviewed.

A common, powerful group of activators are those included under the concept of stress. 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 'milieu interieur', formed by organic liquid that surrounds all of the tissue elements. Cannon elucidated 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' (92). He describes a 'critical stress' level that produces a 'breaking strain' that results in failure to maintain homeostasis, and he adopts the terms 'stress' and 'strain' as they are used in physics. Selye extended Cannon's concept of homeostasis to include the responses mediated by the HPA axis and proposed a new concept of stress, 'general adaptation syndrome, or GAS'; a single stereotypic response elicited by any demand upon the body (93). For scientific purpose, he defined stress 'as the state which manifests itself by the GAS'.

As the homeostasis is constantly threatened by internal or external adverse factors, stressors, stress is usually defined as a state of threatened homeostasis (17). There are physical stressors such as cold, trauma, fever and infection; psychological stressors such as social subordination, anxiety and depression (94).

Traits of anxiety and depression have a predictive association with visceral obesity in both men and women (55,56). Furthermore, alcohol consumption and smoking are common among subjects with elevated WHR (51,52). In addition, we have recently identified a number of psychosocial and socioeconomic handicaps in this condition (51,52). The most prominent factors are divorce, solitude, poor economy and low education, unemployment, and problems at work when employed. Interestingly, socioeconomic inequality and low educational have recently been shown to be associated with elevated stress-related cortisol secretion as well as visceral obesity (95). Moreover, we have identified a subgroup of elevated WHR and D, where a blunted dexamethasone response is found, associated with traits of anxiety and depression as well as personality disorders (57,96).

It has been suggested that persistent psychosocial and socioeconomic handicaps constitute a base for stress, resulting in frequent challenges of the HPA axis (43). Although biologically plausible, this hypothesis has been difficult to study in humans. In primates other than humans, a diminished feedback regulation of the cortisol secretion, suppression of the reproductive axis, and depressive behaviour follow exposure to standardized, moderate psychosocial stress (97,98). Moreover, such social stress is associated with visceral obesity, insulin resistance, dyslipidaemia, hypertension and coronary artery atherosclerosis (97,98). Thus, these results bear a striking resemblance to that of humans subjected to psychosocial stress, followed by visceral obesity with metabolic syndrome. These studies then provide a solid experimental groundwork for the hypothesis that psychosocial stress and socioeconomic subordination is indeed inducing the metabolic syndrome.

CONCLUSIONS

The concept of a neuroendocrine background to visceral obesity and the metabolic syndrome has been confirmed and strengthened considerably as well as modified by the recently obtained results presented in this overview. Above all, the multiple features of this syndrome have been possible to describe in terms of stages of the HPA axis perturbations and other associated endocrine abnormalities. A truly striking end result is the powerful interaction of the HPA axis with human health and disease (99). Visceral obesity has a remarkable predictive power for prevalent diseases such as type 2 diabetes, CVD, stroke, gallbladder disease, sleep apnoea, hypertension, dyslipidaemia and insulin resistance (relative risk ≥ 3).

Psychosocial and socioeconomic impairments are most likely important triggers for the perturbations of the HPA axis observed, and may have a particularly strong impact on individuals with a predisposing genetical vulnerability.

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