Obesity and Hormonal Abnormalities

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INTRODUCTION

Obesity is associated with multiple alterations in the endocrine system, including abnormal circulating blood hormone concentrations, which can be due to changes in the pattern of their secretion and/or metabolism, altered hormone transport and/or action at the level of target tissues. In recent years a great stimulus in both basic and clinical research has, on one hand, produced a great deal of knowledge on the pathophysiology of obesity, and, on the other, led to the discovery of new hormones, such as leptin (1) and orexins (2).

This chapter reviews the main alterations in the classic endocrine systems, specifically those related to the hypothalamic-pituitary-gonadal (HPG) axis, the growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis, and the hypothalamic-pituitary-adrenal (HPA) axis. The discussion will focus on human endocrinology, and animal studies will be referred to only when relevant to the organization of current knowledge. Several other endocrine systems will not be discussed, and readers are referred to extensive recent reviews in the field (3,4).

The recent discovery of the product of the ob gene, leptin, has pointed to the role of adipose tissue as an endocrine organ, capable of interacting with the central nervous system and other peripheral tissues by an integrated network, mainly devoted to the regulation of the energy balance and fuel stores. The impressive growth of knowledge that has followed the discovery of leptin in 1996 is under continuous investigation. Other chapters of this book review this exciting topic, which will probably radically modify our clinical and therapeutic approach to obesity and related metabolic disorders in the next few years.

THE HPG AXIS IN FEMALES (Table 17.1)

Sex Steroid and Gonadotropin Concentration and Metabolism

An increase in body weight and fat tissue is associated with several abnormalities of sex steroid balance in premenopausal women. They involve both androgens and estrogens and their main transport protein, sex hormone-binding globulin (SHBG). Changes in SHBG, which binds testosterone and dihydrotestosterone (DHT) with high affinity and estrogens with lower affinity, also lead to an alteration of androgen and estrogen delivery to target tissues. The concentrations of SHBG are regulated by a complex of factors, which include estrogens, iodothyronines and growth hormone (GH) as stimulating, and androgens and insulin as inhibiting factors (5). The net balance of this regulation is probably responsible for decreased SHBG con-
Table 17.2 Main alterations of the hypothalamic-pituitary-gonadal axis in obese women

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of obesity on sex hormones</td>
<td>Increased SHBG-bound and non SHBG-bound androgen production rate and metabolic clearance rate</td>
</tr>
<tr>
<td></td>
<td>Reduced SHBG synthesis and concentrations</td>
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<tr>
<td></td>
<td>Increased percentage free testosterone fraction</td>
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<td></td>
<td>Normal gonadotropin secretion</td>
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<td></td>
<td>Increased estrogen production rate</td>
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<tr>
<td></td>
<td>Altered active/inactive estrogen balance</td>
</tr>
<tr>
<td>Impact of central obesity</td>
<td>Worsened androgen imbalance</td>
</tr>
<tr>
<td>Obesity, hyperandrogenism and PCOS</td>
<td>Treatment with androgens increases visceral fat in postmenopausal women</td>
</tr>
<tr>
<td></td>
<td>Obesity may have a pathogenetic role in the development of hyperandrogenism in PCOS</td>
</tr>
<tr>
<td></td>
<td>Obese women with PCOS have a prevalence of visceral fat distribution</td>
</tr>
<tr>
<td></td>
<td>Hyperinsulinemia represents a pathogenetic factor of hyperandrogenism</td>
</tr>
<tr>
<td></td>
<td>The metabolic syndrome is part of the obesity–PCOS association</td>
</tr>
<tr>
<td>Effects of weight loss</td>
<td>In simple obesity, improvement of androgen and SHBG imbalance</td>
</tr>
<tr>
<td></td>
<td>In obese women with PCOS reduction of hyperinsulinemia and insulin resistance, hyperandrogenism, and improvement of all clinical features, including fertility rate</td>
</tr>
</tbody>
</table>

PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin.

centrations in obesity, in inverse proportion to the increase in body weight (4,5). Body fat distribution has important effects on SHBG concentrations in obese women. In fact, those with central obesity usually have lower SHBG concentrations in comparison to their age- and weight-matched counterparts with peripheral obesity (6). Insulin seems to play a dominant role in this context. Numerous epidemiological studies have, in fact, demonstrated a significantly negative correlation between insulin and SHBG blood levels, suggesting a cause–effect relationship (7). Moreover, studies in vitro have shown that insulin inhibits SHBG hepatic synthesis (8), and suppression (9) or stimulation (10) of insulin secretion in vivo has been found to be inversely associated with changes in SHBG concentrations, at least in hyperandrogenic obese women. Not surprisingly, reduced SHBG concentrations are therefore commonly associated with obesity, particularly in the central phenotype, type 2 diabetes, hyperandrogenic states such as polycystic ovary syndrome (PCOS), and cardiovascular atherosclerotic diseases (11), all conditions characterized by hyperinsulinemia and insulin resistance. On the other hand, not all obese women have reduced levels of SHBG, in spite of similar circulating androgen and estrogen concentrations, similar body weight and pattern of fat distribution. It has been suggested, for example, that dietary factors may help to explain these discrepancies. In fact, a significantly negative correlation has been found in premenopausal women between lipid intake and SHBG levels (12). Moreover, experiments performed in men have demonstrated that high lipid intake significantly decreased SHBG concentrations, although contradictory data have been reported by others (see reference 12 for review).

Although the urinary excretion rate of 17-ketosteroids may be higher than normal in obese women (4), the levels of the main androgens are usually high only in obese women with amenorrhea and are normal in those with regular menstrual cycles (12). Gonadotropin secretory dynamics also appear to be normal in eumenorrheic obese women (4). The reduction of SHBG increases the metabolic clearance rate of circulating SHBG-bound steroids, specifically testosterone, DHT and androstane 3, 17β-diol (3A-diol), which is the principal active metabolite of DHT (13). However, this is compensated for by elevated production rates. The metabolism of the androgens not bound to SHBG is also modified by obesity. In fact, both production rates and metabolic clearance rates of dehydroepiandrosterone (DHEA) and androstenedione are equally increased in obesity (14,15), so that no difference in blood concentrations of the hormones is usually found in comparison to normal-weight individuals. Androgen production and metabolism may also show several differences in relation to the pattern of body fat distribution. Kirschner et al. (15), for example, found that premenopausal women with
central obesity had higher testosterone production rates than those with peripheral obesity, whereas no differences in androstenedione and DHT production rate values were found. Accordingly, metabolic clearance rates of testosterone and DHT were significantly higher in the former than in the latter. The maintenance of normal circulating levels of these hormones in obesity suggests the presence of a servo-mechanism of regulation which adjusts both the production rate and the metabolic clearance rate of these hormones to body size. In women with obesity, the rates of androgen production increase but, due to the appreciable quantity of circulating blood passing through the adipose tissue, androgens may be cleared (metabolized) not only in the liver but also in the fat. In turn, this will result in a reduction in hormone uptake by androgen-sensitive tissues. Although speculative, this hypothesis may explain why most obese women seem to be protected against the biological effects of excessive androgen production, such as hirsutism and menstrual disturbances (13).

Obesity can also be considered a condition of exaggerated estrogen production. It has been demonstrated that the conversion of androgens to estrogen in peripheral tissues is significantly correlated with body weight and the amount of body fat (16). Several other factors can contribute to this condition of ‘functional hyperestrogenism’ (12). Due to reduced SHBG synthesis and lower circulating SHBG concentrations in obesity, the free estradiol fraction increases, thus increasing exposure of target tissues to this hormone. Moreover, the metabolism of estrogens is altered in obese women. A decreased formation of inactive estradiol metabolites, such as 2-hydroxyestrogens, which are virtually devoid of peripheral estrogen activity, is observed, together with a higher than normal production of estrone sulfate (which represents an important reservoir of active estrogens, particularly estrone), due to the concurrent reduction of its metabolic clearance and increased production rate. The final result of these metabolic derangements on estrogens is an increased ratio of active to inactive estrogens in obese women. In spite of these alterations, blood estrogen concentrations are usually normal or only slightly elevated in both premenopausal and postmenopausal obese women (3,4). This may be related to the fact that enlarged body fat may act as deposits for excess formed estrogen, thus contributing to maintain normal circulating hormone concentrations.

Most sex steroid and SHBG alterations can be improved by reducing body weight (17).

The Impact of Body Fat Distribution

Due to the greater reduction of SHBG concentrations, percentage free testosterone fraction tends to be higher in centrally obese women than in those with peripheral obesity (18). Moreover, there are hardly ever systematic differences in the concentrations of principal C19 androgens between women with central and peripheral obesity, although the former may have higher androstenedione levels than the latter (19). This may be due to the fact that androgen production rates are higher in women with central obesity than in their peripheral counterparts (see above). An inverse correlation exists between waist-to-hip ratio (WHR) (or other indices of body fat distribution) and testosterone or SHBG concentrations, regardless of body fatness and body mass index (BMI) (18). Therefore, a condition of ‘relative functional hyperandrogenism’ may be present in women with the central obesity phenotype. This may play an important role in the development of visceral fat deposits. Androgen receptors are expressed in the adipose tissue, with a higher density in intra-abdominal than subcutaneous deposits, at least in rats (20). In concert with GH and catecholamines, testosterone activates the lipolytic cascade particularly in the visceral adipocytes, thus favoring increased free fatty acid release (20). These events are suggested as participating in the development of insulin resistance and compensatory hyperinsulinemia, both conditions invariably associated with central obesity. Increased insulin levels can in turn produce an inhibition of SHBG synthesis, which further aggravates the androgen imbalance. Since hyperinsulinemia per se appears to play a role in the development of visceral fatness, hyperinsulinemia and ‘functional hyperandronism’ in the central obesity phenotype may participate in a coordinated fashion to increase visceral fat deposits in obese women. This is further supported by the finding that exogenous androgen administration in obese postmenopausal women has been shown to cause a significant gain in visceral fat (as measured by computed tomography scan) and a relatively greater loss of subcutaneous fat in comparison with placebo (21).
Obesity and Hyperandrogenism in Premenopausal Women: a Link with the PCOS

Approximately half the women with PCOS are overweight or obese (12). This association has aroused a great deal of interest in recent years, particularly since the discovery that PCOS women are often hyperinsulinemic and that the degree of hyperandrogenism may be positively and significantly correlated with that of hyperinsulinemia (10). The association between obesity and hyperandrogenism develops during puberty, and common pathogenetic mechanisms primarily appear to involve a dysregulation of insulin secretion and action and also of the GH/IGF-I system (22). Recently, however, it has been suggested that in obese women with PCOS, higher than normal ovarian secretion of androgens is associated with birthweight and maternal obesity, suggesting that intrauterine factors may play a role in the development of the syndrome later in life (23). Premenopausal women with PCOS are clinically characterized by several signs and symptoms related to hyperandrogenism and hyperinsulinemia, including chronic anovulation, hirsutism and acne. Hyperandrogenism, hyperinsulinemia and insulin resistance and all clinical features tend to be more severe in PCOS women with abdominal body fat distribution (24). Altered lipid profile represents another associated metabolic characteristic.

Pathophysiological aspects of the association between obesity and PCOS have been extensively reviewed in recent years (12,25,26). There may be various mechanisms by which obesity may influence hyperandrogenism in premenopausal women with PCOS. The pivotal role of insulin was first suggested on the basis of the significant positive correlation observed between the degree of hyperandrogenism and that of hyperinsulinemia in women with PCOS (9). In vitro studies have subsequently demonstrated that insulin is capable of stimulating androgen secretion by the ovaries, reducing aromatase activity in peripheral tissues and, finally, reducing SHBG synthesis in the liver (9,26,27). In vivo, numerous studies have demonstrated that both acute and chronic hyperinsulinemia can stimulate testosterone production and that suppression of insulin levels can conversely decrease androgen concentrations (9,26). The fact that hyperinsulinemia and insulin resistance are invariably associated with obesity and, particularly, abdominal-visceral obesity, represents the basis for the hypothesis supporting its role in the development of hyperandrogenism in PCOS women. Sufficient data demonstrate that suppression of insulin levels by diet (28,29) or chronic insulin sensitizing agent administration, such as metformin (23), troglitazone (30), or d-chiro inositol (31) can improve not only the hyperandrogenic state but also the degree of hirsutism and the fertility rate. These data obviously add further emphasis to the role of obesity-related hyperinsulinemia as a co-factor responsible for increased androgen production in obese PCOS women.

As reported above, obesity is associated with supranormal estrogen production. Since estrogens exert a positive feedback regulation upon gonadotropin release, increased ovarian androgen production in obese PCOS women could be partly favored by increased luteinizing hormone (LH) secretion secondary to prevailing hyperestrogenemia (32). Obesity, as well as PCOS, is also characterized by increased opioid system activity, and studies in vitro and in vivo have shown that β-endorphin is able to stimulate insulin secretion. Moreover, the administration of β-endorphin can reduce LH release at the hypophyseal level in normal but not in PCOS women (33). The possibility that increased opioid activity may favor the development of hyperinsulinemia and, in turn, of hyperandrogenism, is further supported by the finding that both acute and chronic administration of opioid antagonists, such as naloxone and naltrexone, suppresses both basal and glucose-stimulated insulin blood concentrations in a small group of obese women with PCOS and acanthosis nigricans (34). Finally, there are theoretical possibilities that diet may play some role in the development of the obesity–PCOS association, although very few studies have addressed this issue. In fact, a higher than usual lipid intake has been described in PCOS women by some authors (35). Mechanisms by which high lipid intake may be responsible for altered androgen balance in susceptible women with obesity and PCOS have been summarized above.
Table 17.2  Main alterations of the hypothalamic-pituitary-gonadal axis in obese men

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of obesity on sex hormones</td>
<td>Reduced testosterone (free and total), and C19 steroids</td>
</tr>
<tr>
<td></td>
<td>Reduced SHBG concentrations</td>
</tr>
<tr>
<td></td>
<td>Reduced luteinizing hormone secretion</td>
</tr>
<tr>
<td></td>
<td>Increased estrogen production rate</td>
</tr>
<tr>
<td></td>
<td>Altered aromatase activity (?)</td>
</tr>
<tr>
<td>Impact of body fat distribution</td>
<td>Men with hypogonadism have typically enlarged visceral fat depots</td>
</tr>
<tr>
<td></td>
<td>Relationship with waist-to-hip ratio (and other indices of fat distribution)</td>
</tr>
<tr>
<td></td>
<td>Association between androstane 3, 17β-diol glucuronide and visceral fatness</td>
</tr>
<tr>
<td>Effects of weight loss</td>
<td>Improved sex hormone imbalance (increase of testosterone)</td>
</tr>
<tr>
<td>Effect of testosterone therapy</td>
<td>SHBG can be restored to normal when near-normal body mass index is achieved</td>
</tr>
<tr>
<td></td>
<td>Reduction of visceral fat</td>
</tr>
<tr>
<td></td>
<td>Improvement of all parameters of the metabolic syndrome</td>
</tr>
</tbody>
</table>

SHBG, sex hormone-binding globulin.

Effects of Weight Loss and Reduction of Insulin Concentrations in Obese Hyperandrogenic Women with PCOS

There is long-standing clinical evidence concerning the efficacy of weight reduction upon both the clinical and endocrinological features of obese women presenting PCOS. Reduction of hyperandrogenemia (namely testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEA-S)) (28,29) appears to be the key factor responsible for these effects. However, weight loss primarily improves insulin sensitivity and reduces hyperinsulinemia, and changes in testosterone and insulin concentrations are significantly correlated, regardless of body weight variations (28,29). Recent studies have suggested that hyperinsulinemia may be responsible for increased activity of the ovarian cytochrome P450c17 system, which has been implicated in ovarian hyperandrogenism in many PCOS women (36). Reduction of insulin concentrations by diet (37), metformin (27), or d-chiro inositol (31) has been demonstrated to reduce this enzyme activity and, consequently, ovarian androgen production. Finally, weight loss and/or insulin sensitizers also significantly improved ovulation and fertility rate (28,29,31,37), further supporting the role of hyperinsulinemia in the pathogenesis of hyperandrogenism in women with obesity and PCOS. The effects of dietary-induced weight loss on androgen levels (except SHBG) seem to be peculiar to obese hyperandrogenic women, since they have not been reported in non-PCOS obese women (17).

THE HPG AXIS IN MALES (Table 17.2)

Sex Steroid and Gonadotropin Concentration and Metabolism

Contrary to what occurs in obese women, with increasing body weight testosterone (total and free) blood concentrations progressively decrease in obese men (36). Reduced testosterone levels are associated with a progressive decrease of SHBG concentrations as body weight increases (38). Spermatogenesis and fertility are not affected in the majority of obese men, although they may be reduced in subjects with massive obesity (3). Serum testosterone is also inversely correlated with body weight in men with Klinefelter’s syndrome (3), thus supporting the causal relationship between obesity and hypotestosteronemia. Serum levels of other sex steroids have also been examined in obese men. Androstenedione concentrations are usually normal or slightly reduced (39) and are not correlated with the degree of obesity (4). Likewise, concentrations of DHT are usually normal (4). Other C19 steroids, such as DHEA and 3 A-diol and androstenediol (Δ5-diol), may be reduced in obesity (39). As previously reported for women, estrogen production rates are increased in male obesity in proportion to body weight, and blood concentrations of all major estrogens, particularly estrone, may be normal (3,4) or slightly increased (4). Altered estrogen metabolism in obesity presumably reflects the aromatase activity of the adipose tissue, which is responsible for active conversion of androgens into estrogens.
Gonadotropin secretion is also impaired in obesity. In fact, pulsatility studies have shown that obese men have a reduced LH secretory mass per secretory burst without any change in burst number, implying a reduction of total LH secretion from the pituitary, probably due to impaired secretion of the gonadotropin releasing hormone at the hypothalamic level (40). The absence of clinical signs of hypogonadism can be explained by the fact that the testosterone free-fraction represents only 2% of total testosterone, and that obesity predominantly affects circulating bound testosterone, due to the concurrent decreases of SHBG production.

The Impact of Body Fat Distribution

There are contradictory data on the relationship between body fat distribution and T in male obesity. Although some clinical (41) and epidemiological (42) studies found an association between testosterone and WHR values, others in which anthropometry (43) or magnetic resonance (44) were used failed to confirm these results. This suggests that the relationship between sex steroids and WHR may be the result of the shared covariance of WHR and total adiposity, rather than a direct relationship. This is not surprising, since obesity in males is almost always associated with a parallel increase in abdominal and visceral fat, which means that the central distribution of body fat in males depends on the actual presence of obesity. Other studies confirmed that reduction of C19 steroid precursors, such as DHEA, androstenedione, Δ5-diol, is predominantly associated with body fatness rather than with excess visceral fat accumulation (39). Conjugation of steroids with glucuronic acid has been suggested to play a major role in the intracellular levels of unconjugated steroids as well as their biological activity. Recent studies have shown that 3A-diol glucuronide (3A-diol-G) levels are significantly higher in obese men, particularly in those with the visceral phenotype (39). Since glucuronide conjugates have been considered better markers of peripheral androgen metabolism than circulating free steroids, the association between 3A-diol-G and visceral fatness suggests that increased visceral adipose tissue accumulation is a condition in which steroid metabolism is altered (45).

Hypotestosteronemia in male obesity thus appears to be largely justified by the coexistence of peripheral (i.e. reduced SHBG synthesis) and central (i.e. reduced LH secretion) factors. On the other hand, both SHBG and testosterone are significantly and negatively correlated with insulin levels, even after adjusting for BMI and WHR values (43). The inverse relationship with SHBG can be easily explained by the fact that insulin inhibits SHBG synthesis in the liver. A confirmatory role for the insulin effect in vivo has been reported, since suppression of insulin concentrations by diazoxide has been found to increase circulating SHBG in both normal-weight and obese individuals (46). The inverse relationship between testosterone and insulin deserves further consideration. In fact, low testosterone levels can be found in streptozotocin-induced diabetic rats (47) and in males with type 1 diabetes (48). In insulin-deficient rats and humans insulin replacement restores testosterone concentrations to normal (47). In obese men, moderate hyperinsulinemia, such as that obtained during a hyperinsulinemic euglycemic clamp, increased testosterone concentrations, whereas suppression of insulin by short-term diazoxide administration produced the opposite phenomenon (49). Taken together, these data support the concept that insulin may have a ‘direct’ stimulatory effect on testosterone production, similar to that demonstrated in women. Therefore, reduced testosterone levels in obese men appear to result from several complementary factors, including lower gonadotropin secretion and the balanced effects of insulin on SHBG (inhibition) and testosterone (stimulation).

The Effects of Weight Loss and Testosterone Replacement Therapy

Weight reduction by both dietary intervention or surgical procedures can increase testosterone and SHBG concentrations, provided substantial weight loss is achieved (3). When massively obese men return to a near-normal BMI, SHBG concentrations fall within the reference values for normal-weight individuals (50). Although there are no kinetic data on estrogen production following weight loss in obese men, it is likely that estrogen metabolism and peripheral production improve as weight loss increases.

Correction of hypotestosteronemia can also be
Table 17.3  Main alterations of the growth hormone/insulin-like growth factor 1 (GH-IGF-I) axis in obesity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of obesity on GH</td>
<td>Reduced GH levels in proportion to body fat&lt;br&gt;Blunted response to any stimuli (including GHRH, GHRP-6 superanalog, etc.)&lt;br&gt;Reduced pituitary GH secretion&lt;br&gt;Increased GH metabolic clearance rate</td>
</tr>
<tr>
<td>Relationship with body fat distribution</td>
<td>Children and adults with GH deficiency typically have visceral obesity</td>
</tr>
<tr>
<td>Effect of obesity on the IGF-I system</td>
<td>IGF-I concentration normal or reduced (particularly in visceral obesity)&lt;br&gt;Increased free IGF-I fraction</td>
</tr>
<tr>
<td>Effects of weight loss</td>
<td>Improvement of basal and stimulated GH levels (in proportion to body fat loss)&lt;br&gt;Possible effects of nutrition on GH secretion</td>
</tr>
<tr>
<td>Effect of GH replacement therapy</td>
<td>Reduction of visceral fat, in both GH-deficient (children and adults) patients and in obese individuals</td>
</tr>
</tbody>
</table>

THE GH/IGF-I AXIS (Table 17.3)

Basal GH Levels and Secretion and Dynamic Studies

Basal GH levels are markedly reduced in obesity (52,53). This is particularly due to a significant reduction of GH secretory burst mass in the pituitary (52). The extent of this alteration appears to be inversely proportional to the excess body fat (4). Indirect evidence for this is that in subjects with increased body weight due to enlarged lean body mass, such as body builders, GH output and peripheral concentrations are not reduced and GH response to insulin-induced hypoglycemia is in fact normal. Obese subjects are also characterized by blunted GH secretion to all stimuli of GH release, including GHRH, insulin-induced hypoglycemia, L-dopa, arginine, glucagon, exercise, opioid peptides, clonidine, nicotinic acid, or states such as deep sleep (3,54).

Mechanisms responsible for reduced GH levels in obesity are probably multiple. Studies performed in both rhesus monkeys (55) and humans (53) have shown that GH metabolic clearance rate is increased in obesity, in proportion to body weight. The blunted response to growth hormone releasing hormone (GHRH) rules out the possibility that a hypothalamic GHRH deficit may be responsible for reduced GH in obesity. Short-term fasting increases GH levels in obese subjects regardless of body weight loss (56), thus suggesting that GH deficiency in obesity may be a functional reversible state. Pre-treatment with the cholinergic agonist pyridostigmine (57), which suppresses endogenous somatostatin, improves GH release, indicating that enhanced somatostatinergic tone may be responsible, at least in part, for pretreatment reduced GH levels. However, when eliminating the presumed higher than normal somatostatin tone with pyridostigmine, the GH response in obese individuals after any stimuli is still lower than normal (57). GHRP-6 is a potent synthetic exapeptide which specifically stimulates GH release in a dose–response fashion, by interacting with specific hypophyseal and hypothalamic receptors. GH response to GHRP-6 or other peptides of the same family can be decreased by pretreatment with GHRH antiserum, which indicates a degree of dependency of the GHRP-6 action on GHRH. Recent studies have shown that GH response to GHRP-6 was almost twice that induced by GHRH, regardless of cholinergic stimulation by pyridostigmine, and that the combination of these peptides elicited the largest GH discharge ever seen after any stimulus (54). Therefore, other than increased somatostatinergic tone, impaired GH secretion in obesity appears to be a functional reversible state, due to still undefined altered somatotrophic function. Whether GHRH resistance or other mechanisms acting at the pituitary...
levels are co-responsible for blunted GH release in obesity remains to be investigated.

Other factors have been implicated in reducing GH levels. Obesity is a condition of altered and supranormal free fatty acid (FFA) production. Increased FFAs are postulated to inhibit basal GH secretion, by mechanisms independent of effects on somatostatinergic tone (3). This is further supported by the fact that FFA inhibition by antilipolytic agents such as acipimox have been demonstrated to potentiate GH responsiveness to GHRH, with or without pyridostigmine pretreatment (58).

Sex steroids, specifically testosterone and estradiol, have positive effects on GH secretion (3) probably by influencing the pulsatile mode of GH release (52). Basal GH secretory bursts, which are reduced in obesity, are positively correlated with estradiol and testosterone concentrations (50), which further indicates a close relationship between sex steroid imbalance and GH secretory dynamics in the obese state.

Serum (IGF-I) Levels

Levels of IGF-I in obesity have been variously reported to be increased, normal, or decreased (3,4). However, although obese children have lower than normal GH levels in basal conditions and after stimulatory testing, they grow normally, which suggests that IGF-I action in the target tissues for growth is indeed adequate for growth and development before, during, and after puberty (3). Interestingly, it has been found that free IGF-I levels are actually increased in obese subjects (59). An increase in free IGF-I levels could be involved in the decline in GH levels with increasing body fat, via feedback inhibition of GH secretion at the pituitary level. Serum IGF-I levels are particularly reduced in subjects with visceral obesity (60) and an inverse relationship has been found with the amounts of visceral fat, independent of total fat mass (61) in a cohort of subjects ranging from normal weight to obesity. Since insulin regulates IGF-I metabolism via its stimulatory effects on the synthesis of IGF binding protein 1 (IGF-BP-1), altered IGF-I in obesity, particularly the visceral phenotype, may reflect prevailing hyperinsulinemia in the blood circulation.

Effect of Weight Loss

Weight reduction significantly improves basal and stimulated GH levels, in proportion to the amount of body weight lost (3). However, there are no studies confirming that weight loss can completely restore GH secretion to normal. This is probably due to the fact that it is difficult to regain a normal weight, particularly in subjects with massive obesity. On the other hand, nutrition itself is an important factor regulating GH secretion and metabolism. As mentioned above, short-term fasting can partially restore baseline and stimulated GH concentrations (56). Starvation is associated with increased GH levels. Therefore, in conditions of energy deficit, absolute or relative GH increase appears to represent an adaptive mechanism by which the body provides fuels from lipolytic pathways to support energy balance. Since weight loss in obese patients can be achieved by varying degree of energy restriction, it would be interesting to investigate how much the positive effect of partial weight loss on GH secretion is due to a reduction of body fat and how much to energy restriction per se, particularly in carbohydrates.

Effects of GH Administration

GH has a potent lipolytic activity and therefore, suppressed GH levels in obesity can be viewed as an unbalanced lipogenetic condition, which could probably be responsible for the perpetuation of the obese state once established. In fact, obese subjects have elevated insulin levels as a consequence of the insulin resistance state with respect to carbohydrate metabolism, but the adipose tissue remains sensitive to the antilipolytic effects of insulin. Evidence from animal and human studies supports the hypothesis that GH administration in obesity may stimulate lipolytic pathways and can provide a valuable adjunct to diet in inducing weight loss. Ventromedial hypothalamic lesions in rats produce obesity, hyperinsulinemia and decreased GH secretion. When administered to hypophysectomized ventromedial-lesioned rats, GH prevents both hyperphagia and development of obesity (62). Genetically obese Zucker fa/fa rats also have decreased GH secretion and GH treatment results in reduced lipid deposition (62). In GH-deficient children, many of whom
**Table 17.4** Main alterations of the hypothalamic-pituitary-adrenocortical axis in obesity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ACTH/cortisol in obesity</td>
<td>Increased cortisol metabolic clearance rate</td>
</tr>
<tr>
<td></td>
<td>Increased ACTH pulse frequency</td>
</tr>
<tr>
<td></td>
<td>Normal cortisol axis diurnal rhythm</td>
</tr>
<tr>
<td></td>
<td>Normal 24-hour ACTH/cortisol concentrations</td>
</tr>
<tr>
<td></td>
<td>Reset to lower resilient axis (?)</td>
</tr>
<tr>
<td></td>
<td>Altered cortisol suppression after overnight dexamethasone (?)</td>
</tr>
<tr>
<td>Effects of body fat distribution</td>
<td>High glucocorticoid receptor density in the visceral adipose tissue</td>
</tr>
<tr>
<td></td>
<td>Altered cortisol production in the visceral adipose tissue (increased/decreased activity of the 11β-HSD)</td>
</tr>
<tr>
<td></td>
<td>Reduced ACTH pulse amplitude</td>
</tr>
<tr>
<td></td>
<td>Positive relationship between visceral fat and daily urinary free cortisol excretion rate</td>
</tr>
<tr>
<td></td>
<td>Lower suppression to submaximal dexamethasone administration (?)</td>
</tr>
<tr>
<td></td>
<td>relationship with perceived stress-dependent free salivary cortisol levels</td>
</tr>
<tr>
<td></td>
<td>Increased CBG binding capacity in parallel to insulin resistance</td>
</tr>
<tr>
<td>Dynamic studies</td>
<td>Increased ACTH/cortisol response to CRH, CRH + AVP, ACTH, acute stress,</td>
</tr>
<tr>
<td></td>
<td>insulin-induced hypoglycemia (?), meals (?)</td>
</tr>
<tr>
<td></td>
<td>Increased ACTH response to CRH + AVP (normal-weight individuals: reduced) during mild increase of NE blood levels (reference 94)</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropin; CBG, corticosteroid-binding globulin; CRH, corticotropin-releasing hormone; AVP, arginine vasopressin.

are obese, GH administration reduces body fat (63). The same occurs in subjects with adult GH deficiency (64), and in elderly subjects who underwent therapy with GH to increase lean body mass and improve fitness (65). Exogenous GH administration also reduced fat stores, particularly in the visceral depots, in GH-deficient adult subjects (66). These effects can be additive to those dependent on diet restriction, but they may also occur in conditions of eucaloric intake (67). Interestingly, the magnitude of this effect appears to be independent of initial body weight and endogenous GH status (67). One limitation of GH administration is related to the possibility that long-term GH treatment worsens glucose tolerance and insulin resistance, although the contrary has been reported by some studies (66). Perhaps the administration of GH in a manner that stimulates normal physiological secretion rather than pharmacological doses would circumvent or lessen its effects on carbohydrate metabolism in the long term.

**THE HPA AXIS (Table 17.4)**

**Similarities Between Visceral Obesity and Cushing’s Syndrome**

Patients with Cushing’s syndrome have typically enlarged visceral fat deposits and show all features of the metabolic syndrome, due to the biological effects of prevailing hypercortisolemia. The main metabolic abnormality of cortisol excess is insulin resistance, which develops by cellular mechanisms that have been largely elucidated (68). Briefly, glucocorticoids inhibit glucose uptake by peripheral tissues, stimulate gluconeogenesis, and cause increased postabsorptive glucose and insulin. In insulin-sensitive tissues, glucocorticoids impair post-receptor insulin function by mechanisms that involve interaction with glucose transporters (68). Treatment of hypercortisolism by pituitary or adrenal surgical procedures can completely reverse these abnormalities.

Subjects with visceral obesity may be characterized by several Cushing-like features, i.e. abdominal striae, buffalo hump, facial plethora, etc., and have associated abnormalities of the metabolic syndrome. Theoretically, these abnormalities may be related, at least in part, to alterations of cortisol metabolism and hyperactivity of the HPA axis.

**ACTH and Cortisol Concentrations in Basal Conditions**

It is well recognized that cortisol metabolism may be increased in obesity. This may be due to the coordinated interference of several factors. First, the
concentrations of corticosteroid-binding globulin (CBG) may be reduced in obesity, although not systematically (3). Moreover, glucocorticoid receptors have been demonstrated in adipose tissue by different techniques, all of which show that they are significantly more dense in visceral than in subcutaneous adipose tissue (69). Finally, adipose tissue can metabolize cortisol to cortisone and vice versa, a reaction that is catalyzed by the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzyme system. Bujalska and coworkers (70) found that the production of cortisol from cortisone in the omental fat taken from normal-weight and obese patients undergoing surgical procedures was significantly higher than in the subcutaneous fat, taken from normal-weight and obese patients, due to the increased expression of the 11β-HSD isoform type 1 (a low-affinity NADP(H)-dependent dehydrogenase/oxoreductase), this activity being further enhanced by tissue exposure to cortisol and insulin. The increased ‘production’ of cortisol could ensure a constant exposure of glucocorticoids to omental tissue, therefore playing a potential role in determining differentiation and mass increase of such a tissue, as recently suggested (71) and, in addition, may represent an inappropriate feedback signal at the neuroendocrine levels, able to modify both the basal activity of the HPA axis and its response to stimulatory and/or inhibitory factors. The concept that obesity may be associated with increased activity of the 11β-HSD has been recently supported by human studies which demonstrated an increased ratio of daily urinary cortisol-to-cortisone metabolite secretion in obese subjects, particularly in those with the abdominal phenotype (72), although controversial findings have also been reported (73).

In unselected obese subjects, normal values have been reported for plasma cortisol, plasma unbound cortisol, 24 h mean plasma cortisol, urinary free-cortisol excretion, and circadian rhythms of plasma and urine cortisol (74). On the other hand, a higher than normal 24 h urine free-cortisol excretion has been reported in women with visceral obesity, and a positive correlation with anthropometric parameters of visceral fat distribution was found (75–77), suggesting that cortisol production may increase as the amounts of visceral fat enlarge.

The impact of obesity on adrenocorticotropic hormone (ACTH) and cortisol pulsatile rhythm has been poorly investigated and available data, which predominantly refer to obese men, often yielded conflicting results. Although several studies reported normal plasma cortisol levels and daily circadian rhythms, others found either lower than normal single samples or lower 24 h integrated cortisol levels in obese men (3). In all these studies, however, ACTH dynamics were not investigated. Studies in obese women are very scarce. Recently, it has been demonstrated that premenopausal women with visceral obesity may have several abnormalities of ACTH (but not cortisol) pulsatile secretion (78), specifically higher than normal ACTH pulse frequency and reduced ACTH pulse amplitude, particularly during the morning, without any significant change in mean basal ACTH blood concentrations. The mechanisms responsible for these alterations are still unclear. Recently it has been demonstrated that a highly significant inverse relationship between rapid fluctuations in plasma leptin and those of ACTH and cortisol exists in normal men, and that obese individuals, in whom higher than normal leptin levels are present, maintain unaltered both leptin diurnal variability and pulsatile secretion (79), with higher pulse height resulting in higher mean daily leptin concentrations in the blood. Therefore one of the central effects of leptin in the central nervous system might be the acute suppression of the HPA axis. Whether increased brain leptin concentrations in obesity may be in some way responsible for altered ACTH pulsatility, particularly in the visceral phenotype, remains, however, to be clarified.

**Effects of Meals on ACTH and Cortisol Concentrations**

Meals are potent stimulators of adrenocortical function. In fact, food ingestion, particularly at noon, elicits sustained cortisol release regardless of its pulsatile rhythm (80). The increase in cortisol concentrations appears to be higher in women with visceral obesity than in those with subcutaneous obesity and controls (78,81,82). Theoretically, this could reflect an altered responsiveness of the adrenals to ACTH in obesity. Whatever the mechanism of action, these findings suggest that women with visceral obesity are inappropriately exposed to supranormal cortisol levels, which, in turn, may have a negative impact on the regulation of postprandial fuel metabolism and on insulin action in peripheral tissues.
The Activity of the HPA Axis: Dynamic Studies

Studies in obese subjects not selected on the basis of the pattern of body fat distribution have demonstrated that both ACTH and cortisol response to corticotropin-releasing hormone (CRH) was either normal or reduced (74) when compared to normal-weight controls. On the other hand, Weaver and coworkers (83) found that obese women representing a wide spectrum from ‘gynoid’ to ‘android’ obesity had significantly higher ACTH response to insulin-induced hypoglycemia with respect to controls, although no significant relationship between fat distribution and hormonal response was reported. Recently, however, several studies have reported data supporting the concept that obese women with visceral body fat distribution may have hyperactivity of the HPA axis (75,76,84). This alteration is characterized by exaggerated ACTH and cortisol response to intravenous administration of CRH alone (76) or combined with arginine vasopressin (AVP) (84), and by higher than normal cortisol response to intravenous ACTH stimulation or acute stress challenge (75,84,85). In addition, visceral obese women also have hyperactivity of the HPA axis to opioid blockade which can be completely reversed by increasing the serotoninergic receptor activation by dexfenfluramine (86). Other studies indicate that obese men also have a higher than normal ACTH (but not cortisol) response to combined CRH/AVP administration and that this alteration may be significantly correlated with the insulin concentrations, regardless of BMI and WHR values (87). In addition, a decrease in the inhibition of cortisol secretion by single low-dose (0.5 mg overnight) dexamethasone administration and an inverse correlation between the decrease of serum cortisol and the WHR has been found by other investigators (88). This supports the concept that increased sensitivity and/or responsiveness by CRH receptors in the brain could be due, at least in part, to the deficient control of CRH receptors by the inhibitory feedback action of glucocorticoids on the system.

The mechanisms responsible for neuroendocrine abnormalities are still unclear and need to be elucidated. First, they could be due to a primary neuroendocrine alteration leading to increased sensitivity to CRH or ACTH-secreting cells or to increased CRH flow towards the pituitary. Another quite convincing theory, however, claims that the HPA hyperactivity may represent part of an altered response to acute and/or chronic stress which can be independent of the mechanisms responsible for feedback regulation (69). Several studies have in fact demonstrated that a similar neuroendocrine adaptation takes place during the reaction behaviour in laboratory animals exposed to various socioenvironmental stressors. For example, Shively and her colleagues (89) exposed cynomolgus macaques to chronic physical and psychological stress, and subsequently showed that the animals developed high visceral fat deposition, which was combined with insulin resistance, hyperinsulinemia and impaired glucose tolerance, adrenal hypertrophy, enhanced cortisol response to ACTH stimulation, altered lipid profiles and incidence of coronary artery atherosclerosis significantly greater than controls. Theoretically, women with visceral obesity may have hyperactivity of the HPA as a consequence of maladaptation to chronic stress exposure. In this model, a key role is represented by the combination of events involving maladaptation to altered coping reaction to chronic stress. In fact, these abnormalities include increased or unbalanced ACTH and cortisol response. Recent data from epidemiological studies by Björntorp’s group appear to be consistent with the hypothesis and with the aforementioned animal data. In fact, they found a strong association between symptoms of mental distress (such as anxiety, depression, etc.), smoking habits and alcoholic consumption, as well as certain psychosomatic diseases and, finally, low socio-economic conditions and abdominal obesity in both males and females (90–93). Furthermore, in a large cohort of middle-aged men they recently demonstrated a significant interaction between diurnal cortisol secretion (measured in saliva) related to perceived stress and several anthropometric, endocrine and metabolic variables (82). Moreover, they found that a non-stressed HPA axis was characterized by decreased cortisol variance, whereas chronically stressed subjects presented decreased cortisol variance, mostly due to evening nadir elevation, morning zenith decrease and inadequate suppression of morning cortisol by overnight dexamethasone (82). In addition, there are data consistent with a dysregulation of the noradrenergic control of the HPA axis during acute mild stress in subjects with obesity, particularly the abdominal
phenotype (94).

All these findings suggest chronic neuroendocrine (at the CRH level?) hyperactivity in stressed individuals and a reset of their HPA axis to a lower resilient state. In addition, they are consistent with aforementioned data from Shively obtained in cynomolgus macaques. On the other hand, much more data are needed to clarify this complex interaction between environmental factors and the pathophysiology of human obesity and related metabolic and cardiovascular comorbidities.

To summarize, there is increasing evidence that the activity of the HPA axis is dysregulated in many obese individuals, particularly those with the visceral phenotype. At least two distinct alterations can be observed. The first, which appears to be central in origin, is characterized by altered ACTH pulsatile secretory dynamic and diurnal chronobiology, and by a hypersensitivity of the HPA axis to different neuropeptides and acute stress events and, possibly, to selected dietary factors. The other appears to be located in the periphery, namely the visceral adipose tissue, which is characterized by elevated cortisol traffic and, probably, by supranormal cortisol production. It is also possible that this last alteration may be responsible, at least in part, for inappropriate feedback signals at the neuroendocrine level and altered ACTH secretion.

CONCLUSIONS

This chapter focuses on the main alterations of the HPG axis, the GH/IGF-I axis and the HPA axis in human obesity. Many of these alterations may have a pathogenetic role in the development of excess body fat, particularly visceral fat, and related metabolic abnormalities. Indirect evidence of this is that all obese subjects with GH deficiency, endogenous hypercortisolism and, in males, hypogonadism, have enlarged visceral fat depots. At variance, a prevalence of visceral body fat distribution is typically associated with hyperandrogenism in women with obesity alone and in those with PCOS. This gender dichotomy obviously needs to be further elucidated. Finally, there are preliminary physiological and clinical studies suggesting that hormonal replacement treatment may have a potential application in the treatment of obesity, particularly the visceral phenotype.

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**Note:** The text above includes a mix of medical and scientific references, likely from a textbook or research paper. It discusses various aspects of obesity, including hormone metabolism, metabolic clearance rates, effects of acute hyperinsulinenemia, treatment of obesity with recombinant human GH, and the impact of obesity on body composition and metabolism. The references are cited in the text, indicating a well-researched and evidence-based approach to the topic.


