Endocrine Abnormalities of Obesity

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Studies have shown that patients with central obesity have increased cortisol secretion, probably because they have increased activity of the hypothalamic-pituitary-adrenal (HPA) axis. A high waist-to-hip ratio (WHR) is associated with low production of sex steroids, such as testosterone in men, and a low rate of secretion of growth hormone. High levels of cortisol and insulin combined with low levels of growth hormone and sex steroid can cause lipid accumulation. These hormonal changes probably produce more deposition of visceral than subcutaneous fat. Patients who are deficient in either testosterone or growth hormone show a reduction in visceral adiposity when their hormone levels are normalized. Stress has been shown to activate the HPA axis and may cause the hormonal changes associated with obesity. Individuals with elevated WHR have indications of high levels of stress and anxiety. Monkeys that were stressed by social disruption were found to have increased cortisol levels and low sex steroid levels. Many of these animals had insulin resistance and visceral adiposity. Stimulants, such as alcohol and smoking, also increase the activity of the HPA axis.

A NUMBER of endocrine abnormalities are associated with obesity. Activation of the hypothalamic-pituitary-adrenal (HPA) axis can cause increased secretion of cortisol and decreased production of growth hormone and sex steroids. These hormonal changes together with a genetic predisposition, may lead to the development of a central or abdominal distribution of body fat.

Corticotrophin-releasing hormone (CRH) stimulates the secretion of corticotrophin (ACTH), which, in turn, stimulates cortisol secretion (Fig 1). A number of studies have looked at blood cortisol levels in relation to obesity, but few have assessed the effect of body-fat distribution on cortisol levels. In one study, urinary cortisol output increased with increasing waist-to-hip ratio (WHR), but the results were inconclusive. The relationship with urinary cortisol excretion rate was stronger for abdominal sagittal diameter, which is a better index of central obesity.[1]

In another study, the adrenal glands were stimulated by ACTH to produce cortisol. Cortisol production was greater in patients who had abdominal obesity compared with patients who had peripheral obesity. ACTH and cortisol secretion rates in response to CRH were more pronounced in individuals who had central obesity compared with those who had peripheral obesity. In studies where the HPA axis was stimulated, by mental or physical stress tests, patients with a high WHR showed a higher response than the lean controls.[1,2]

SEX STEROIDS AND GROWTH HORMONE

The production of sex steroids may be altered in patients with central obesity. Studies have shown that women with a high WHR have increased levels of free testosterone: they are hyperandrogenic.[3] In men, the opposite is true: men with central obesity have, on average, lower levels of testosterone.[4]

Growth hormone is lower in obese patients compared with lean individuals. Insulin-like growth factor (IGF-1) levels are negatively associated with visceral fat and WHR. However, IGF-1 levels are not dependent on total adipose tissue nor the amount of subcutaneous adipose tissue.[5]

It is possible that these hormonal abnormalities could be secondary to the increased activity of the HPA axis, because CRH has been reported to inhibit growth hormone–releasing hormone (GHRH) and gonadotrophin-releasing hormone (GnRH), affecting the production of IGF-1 and sex steroids, respectively (Fig 1).

CENTRAL OBESITY

The endocrine abnormality consists of an increase in cortisol and insulin secretion and a decrease in growth hormone and testosterone secretion. Cortisol and insulin both increase lipid accumulation and diminish lipid mobilization, while growth hormone and testosterone promote lipid metabolism. The combined effect of these hormonal abnormalities is therefore likely to be lipid accumulation.[7]

The hormonal changes have a more pronounced effect on visceral fat deposition than on subcutaneous adipose, probably because there are more cells per unit mass in visceral than subcutaneous adipose tissue. Also, blood flow to visceral adipose is greater so the hormonal effects are magnified. In vitro studies indicate that there are more specific glucocorticoid and androgen receptors in visceral fat than in subcutaneous adipose tissue, again amplifying the effects of these hormonal imbalances.

The effects of insulin and cortisol seem to be balanced by testosterone and growth hormone, in terms of directing visceral fat deposition. Testosterone and growth hormone secretion can diminish with age whilst insulin and cortisol levels often remain normal. This may explain the tendency toward visceral fat accumulation with aging. Men with low testosterone levels and higher visceral fat accumulation have shown a reduction in their visceral adiposity when treated with testosterone. Similarly, when growth hormone was given to growth hormone-deficient patients, their visceral obesity decreased by about 30%.[8]

These hormonal abnormalities may contribute to the development of insulin resistance. High cortisol levels and

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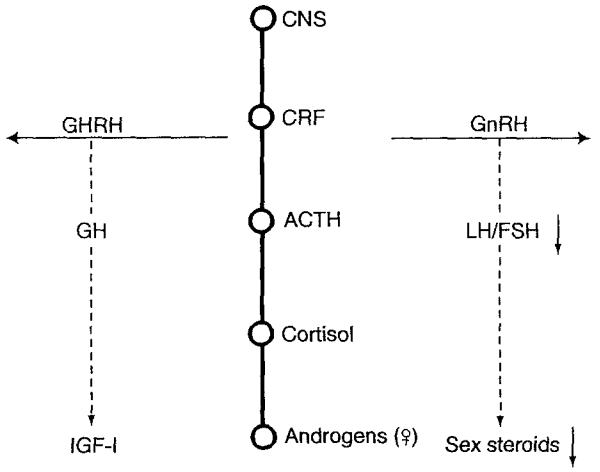

Fig 1. CRF, corticotrophin-releasing factor; GHRH, Growth hormone–releasing hormone; GH, growth hormone; GnRH, Gonadotrophin-releasing hormone; LH, luteinizing hormone; FSH, Follicle-stimulating hormone; IGF-I, insulin-like growth factor.

low testosterone levels in men have been associated with insulin resistance. Central adipose tissue is more sensitive to lipolytic stimuli[9]; therefore, visceral fat could increase circulating levels of free fatty acids (Fig 2).

HPA AXIS STIMULI

The HPA axis is regulated by stimuli, which act on the pathway before CRH. The HPA axis could be sensitized by continuous bombardment from these stimuli.[10] Overactivity of the HPA axis and excess cortisol secretion can also be followed by downregulation of glucocorticoid receptors in the brain controlling the axis.[11] A well-known factor that activates the HPA axis is stress, particularly stress producing feelings of helplessness or defeat. In population studies, men and women with a higher WHR report ill more often, have more frequent peptic ulcers and stomach bleeding, and have more general health complaints. This may indicate a high level of stress or poor coping with stress levels. Psychiatric problems are more common in such women, who also use tranquilizers more often, they feel stressed and report sleepless nights more often than other women. Women with a high WHR often take antidepressant drugs. Stress, anxiety, and depression all activate the HPA axis. This activation and resulting hormonal changes may be involved in the development of visceral adiposity.[12,13]

A high WHR is associated with the use of stimulants, such as alcohol and smoking. Alcohol and smoking increase activity along the HPA axis (Fig 3).[12,13]

Studies into the effects of stress on hormonal levels have been performed in monkeys. The social hierarchy of a monkey colony was deliberately disrupted and monkeys continually placed at the bottom of the social hierarchy developed a helplessness reaction to stress. These highly stressed animals had increased cortisol secretion, large adrenals, low sex steroid levels, and activation of the sympathetic nervous system. In addition, these monkeys had insulin resistance, impaired glucose tolerance, coronary heart disease, and accumulation of visceral fat.[14]

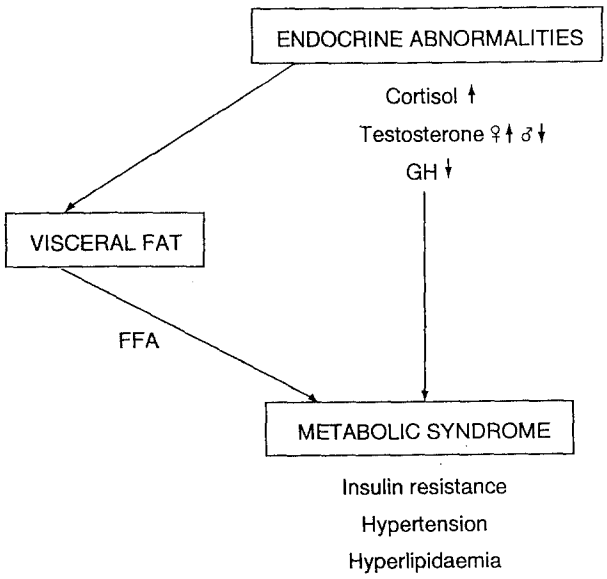

Fig 2. FFA, free fatty acids.

SUMMARY

Stimulation of the HPA axis and neuroendocrine disturbances lead to endocrine abnormalities, such as increased cortisol secretion and decreased production of growth hormone and sex steroids. These hormonal changes may increase the deposition of visceral fat. Stress, anxiety, alcohol, and smoking also contribute to the endocrine abnormalities that promote deposition of the visceral adipose tissue. Visceral obesity, neuroendocrine disturbances, overeating, and physical inactivity may all be involved in the development of insulin resistance, cardiovascular disease, and non–insulin-dependent diabetes mellitus.

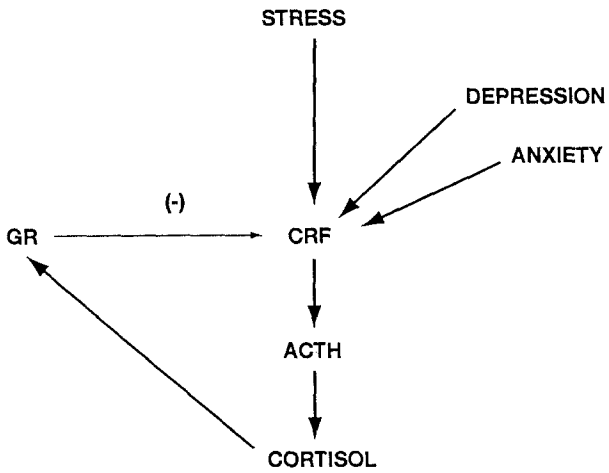

Fig 3. GR, glucocorticoid receptors.

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