NEUROENDOCRINE REGULATION OF THE STRESS RESPONSE

The contributions of neuroendocrine mechanisms in maintaining homeostasis have been discussed individually throughout the previous chapters and in a more integrated approach in the present chapter. Alterations in the environment or in the host that require adaptation involve the synchronized interaction of virtually all aspects of neuroendocrine function that have been described. The adaptation to a biologic, psychosocial, or environmental insult to the host is referred to as the stress response; in the acute setting, it is also termed the "fight or flight" response. It is now clear that in modern life, this stress response can be chronic, with a significant cost to the health of the individual. This wear and tear of chronic adaptation to daily stressors constitutes the allostatic load of the individual; it is the "pathologic" chronic homeostasis through which we achieve stability at the expense of psychosocial and physical well being.

Chronic activation of the mechanisms that restore homeostasis results in excessive and, in some cases, inadequate responses that ultimately alter the function of virtually all organ systems (eg, hypertension, autoimmune disorders, metabolic syndrome) (Figure 10–6). Many of the effects of this dysregulated state are mediated by chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, producing marked alterations in endocrine function, such as the following.

Figure 10–6.
Neuroendocrine responses to chronic or severe stress. Chronic activation of the neuroendocrine response to restore homeostasis influences virtually all organ systems. The short-term activation of these stress-response mechanisms ensures that energy substrates are available to meet the increased metabolic demands of the individual. However, prolonged duration and increased magnitude of these activities lead to erosion of lean body mass and tissue injury. GH, growth hormone; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal; IGF-I, insulin-like growth factor-I; SNS, sympathetic nervous system; TSH, thyroid-stimulating hormone.

**Inhibition of reproduction function**—Enhanced release of corticotropin-releasing hormone (CRH) and β-endorphin suppresses GnRH release directly and indirectly through the release of glucocorticoids.
Glucocorticoids decrease the release of luteinizing hormone and produce gonadotropin resistance at
the gonads. This suppression in gonadal function is evident in patients with anorexia nervosa,
athletes, and ballet dancers.

**Inhibition of the GH-IGF-I axis**—Chronic activation of the HPA axis suppresses GH release and inhibits
the effects of IGF-I at target tissues.

**Suppression of thyroid function**—CRH and cortisol suppress the production of thyroid-stimulating
hormone and inhibit the activity of peripheral 5'-deiodinase, leading to the euthyroid sick syndrome.

**Dysregulation of energy substrate metabolism**—An increase in catecholamines stimulates lipolysis
and decreases triglyceride synthesis in white adipose tissue. In the liver, increased epinephrine levels
stimulate hepatic glycogenolysis and, together with high cortisol levels, increase hepatic glucose
output. High cortisol levels resulting from activation of the HPA increase gluconeogenesis, produce
insulin resistance in peripheral tissues, inhibit the lipolytic action of GH, and inhibit bone osteoblastic
activation (remodeling) by sex steroids. This leads to increases in visceral adiposity and loss of BMD
and lean body mass. This aspect of the stress response may be of particular importance in the
treatment of diabetic patients during stressful periods such as surgery or infection.

**Alterations in the Immune Response**—The significant rise in circulating cortisol levels affects virtually
all aspects of the immune response, including cytokine production, leukocyte trafficking and
recruitment, and production of chemokines. Overall, glucocorticoids exert an anti-inflammatory
response. CRH may have direct proinflammatory effects on cells of the immune system. Activation of the
autonomic nervous system also affects the immune response through effects on neutrophil
demargination and cytokine production.

Short-term activation of these stress-response mechanisms ensures that energy substrates are
available to meet the increased metabolic demands of the individual. However, prolonged duration and
increased magnitude of these activities lead to erosion of lean body mass and tissue injury.
Nevertheless, impaired activation or lack of responsiveness of the HPA and autonomic nervous system
can also be deleterious, as in the case of the critically ill patient. Thus, the overall regulation of the
neuroendocrine responses that mediate the physiologic functions involved in maintaining and restoring
homeostasis is critically important in situations such as illness, trauma, surgery, or fasting.