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To Omer
who helped throughout
and co-authored
chapter 9 -
Best wishes
for his career
and happiness
in life
Paola S. Timiras

Physiological Basis of Aging and Geriatrics

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9

The Adrenals and Pituitary—Stress, Adaptation, and Longevity

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■ INTRODUCTION

The endocrine system, like the nervous system, coordinates physiologic responses to environmental signals to enhance individual survival and reproduction. Since aging often brings about a decline in physiologic function, it is not surprising that, in regard to the endocrine system, old age engenders

- a diminished capacity to adapt to internal and external demands, especially under stress conditions and
- a deterioration of reproductive function in men and a cessation of reproduction in women.

Both in early and late stages of the life span, development and aging are associated with changes in endocrine function, and endocrine function is known to affect hormonal levels. It is clear that cellular and molecular changes occur with senescence, but it is not certain that these changes are responsible for senescence and ultimately death. Nevertheless, it is strongly suspected that hormonal changes influence functional decrements, disabilities, diseases of old age, and the length of the life span (1–4).

In recent years, various tools have been added to the classical, clinical, physiological, and biochemical measurements of endocrine function. New techniques, adopted from the fields of genetic engineering and molecular and structural biology, have provided new advances in the study of mutations in humans and in the use of genetic disruption in transgenic or knockout animals (5,6). These new tools and techniques can fruitfully be applied to the study of physiologic systems, such as the hypothalamo-pituitary-adrenal (HPA) axis discussed in this chapter. The HPA axis includes the cortical and medullary components of the Adrenal Gland: HPA may refer specifically to the HPA Adrenal cortical component and its steroid hormones, and/or to the HPA Adrenal Medullary and its catecholamine neurotransmitter, part of the sympathetic nervous system. The HPA axis is primarily regulated by feed back mechanisms. Also, new technologies for detection of hormonal signaling are being used in the study of growth, development, and reproduction. Thus, mimicking human endocrine pathology through animal gene mutations is providing new insights into endocrine aging.

The section following this introduction discusses the assessment and measurement of endocrine function. The subsequent sections discuss the structure and functions of the adrenal cortex, the adrenal medulla, and the pituitary gland. The last section, entitled Stress and Adaptation, discusses the stress response and its consequences, highlighting the key role of the HPA axis and the mechanisms that regulate adaptation and contribute to survival and reproduction.

■ ENDOCRINE GLANDS, HORMONES, AND CHEMICAL MESSENGERS

The wide distribution, multiplicity, and diversity of hormones acting as chemical mediators in the body partly testifies to the critical role of endocrine regulation of bodily functions (Box 1). This important role certainly applies to the hormones of the HPA axis, which is discussed in this chapter. HPA hormones are responsible for communication among cells within the same organism and between the organism and its surrounding environment. The *hypothalamus*, situated in the midbrain, plays key roles in the regulation of several complex behaviors, such as endocrine, autonomic, and metabolic functions, and circadian rhythms. The *pituitary* (or hypophysis) secretes several hormones that stimulate peripheral targets, either other endocrine glands or specific tissues and organs. The location of the pituitary—in the close vicinity of the hypothalamus with which it articulates through a vascular net, the portal system, and through direct neuronal connections—makes it an intermediary between the nervous and endocrine systems. Among the endocrine glands, the *adrenals* regulate certain aspects of metabolism, behavior, and nervous and immune functions and, thus, play a key role in homeostasis. As with all endocrine glands, the adrenals and pituitary do not act in isolation. They are dependent for their function on neuroendocrine signals, usually initiated in or relayed through the hypothalamus (7–9). The endocrine glands are also dependent on the functional status of the target cells. With aging, changes in endocrine function may depend on changes in the following:

- A single endocrine gland
- Several endocrine glands simultaneously
- Other bodily systems (e.g., nervous, immune, cardio-vascular)
- Body metabolism and composition
- Cellular and molecular responses of target cells and tissues

In many cases, the assessment of a biological construct, such as aging, is sensitive to different experimental designs. These experimental designs may be modified in different ways to suit research needs. Thus, manipulation in experimental animals and diseases in humans, must be carefully considered by the researcher as they may challenge the validity of the results. Among the variables the most frequently included are:

- The influence of stress, disease, medications, and drugs
- The influence of heredity and environment
- The influence of diet and exercise

■ Assessment of Endocrine Function

It is difficult to evaluate endocrine function, and the reasons for this include the following:

BOX 1 *Intercellular Communication by Chemical Mediators*

Endocrine communication is mediated through *hormones secreted by endocrine glands. Secreted hormones are released into the blood circulation and act on distant target cells.* Well-recognized endocrine glands include the pituitary, adrenals, thyroid, parathyroids, pancreas, testes, and ovaries.

Other cells or groups of cells act by paracrine communication. These cells, interspersed among other cells, secrete, in the extracellular fluid, hormones that affect neighboring cells. Examples of paracrine hormone-producing cells are those of the pancreas (with both endocrine and paracrine secretions), the intestinal mucosa, and those producing prostaglandins. Secretory cells may also act by autocrine communication, that is, they secrete chemical messengers that bind to receptors on the very same cell that secreted the messenger. Yet, other cells act by *juxtacrine communication* in which the cells act directly on the neighboring cells.

Some neurotransmitters, such as epinephrine and norepinephrine, are also considered chemical messengers (Chapter 6). Other important messengers such as cytokines, thymic hormones, membrane receptors, and growth or apoptotic factors regulate immune and hematopoietic functions (Chapters 14 and 17). Chemical messengers are for the most part amines, amino acids, steroids, polypeptides, proteins, and, in a few instances, other substances. In different parts of the body, the same chemical messenger can function as a neurotransmitter, a paracrine mediator, and a neurohormone.

- Hormonal actions simultaneously affect several bodily functions
- Hormones regulate responses generated by internal (genes) and external (environmental) signals to promote reproduction and to maintain homeostasis
- The repertory and efficiency of integrative hormonal responses, which are optimally available during adulthood, diminish with advancing age and, thus, compromise strategies for adaptation and survival

The evaluation of endocrine function in humans often relies on relatively noninvasive measurements of blood, urine, and saliva, under basal conditions (resting or steady state) and under stress. Such an assessment often leads to incomplete and erroneous conclusions, since an adequate endocrine evaluation must assess several levels of endocrine action as well as assess the relationship between endocrine and other bodily systems (primarily the nervous and immune systems), hormone–receptor interactions at the target cell, and molecular events inside the cell, as listed in Table 1. Although none of these aging-related changes alone may be sufficient to irrevocably damage physiologic competence, a number of minor changes may desynchronize the appropriate signal at the target cell/molecule and alter hormonal actions. Factors involved in the design of the experimental protocol (e.g., sample size, health, and sex of subjects) to assess endocrine function may also influence the evaluation of changes that occur with old age.

An ideal "global" approach (as outlined above) to the study of endocrine aging is currently very difficult to achieve in humans. This global approach may be implemented more easily in experimental animals and in cultured tissues or cells. Such in vivo and in vitro models represent an important corollary to human studies. As illustrated in Figure 1, changes with aging may occur at all levels of the endocrine system:

- At the endocrine gland level, weight loss with atrophy, fibrosis, and vascular changes occur in most glands, with or without the concomitant occurrence of glandular tumors (adenomas).
- Under basal conditions, blood plasma hormones (free, biologically active hormones or hormones bound to plasma proteins) in humans and in animals are generally not altered in healthy old age, although some hormones (such as sex hormones) decrease significantly.
- Hormone release depends on nervous and environmental stimuli as well as positive and negative feedback from circulating hormones.
- Some hormones act exclusively on one type of target cells, while other hormones act on many cell types (targets) and by several mechanisms. Thus, the same hormone may have different actions in different tissues.
- With aging, one of the many hormonal actions or one of the many targets may be selectively affected while other actions and targets are preserved.

TABLE 1 Factors that Influence an Evaluation of Endocrine Function

Biologic factors
Physiologic factors
Metabolic state
Body composition
Dietary regimen
Physical exercise
Exposure to stress (environmental and psychosocial)
Relationship to other endocrines and bodily systems
The rate of secretion of secretory cells
Transport of the hormones to target cells
Metabolism of the secreted hormones
Metabolites may be more or less biologically active than the secreted hormones (e.g., conversion of T to the more active DHT (Chapter 11) and conversion of T4 to the more active T3 (Chapter 12))
Number and affinity of hormone receptors
Intracellular postreceptor molecular events
Occurrence of disease and use of medications
Experimental design factors
Sample size
Health status of subjects
Conceptualization of age categories
Comorbidity of subjects
Sex of subjects
Subjects under steady state or under stress
Quality, intensity, timing, and duration of stress
Outcome of study
Parameters measured
Duration of parameters measured (long- vs. short-term experiments)

Abbreviations: DHT, dihydrotestosterone; T, testosterone; T4, thyroxine; T3, 3, 5, 3', -triiodothyronine;.

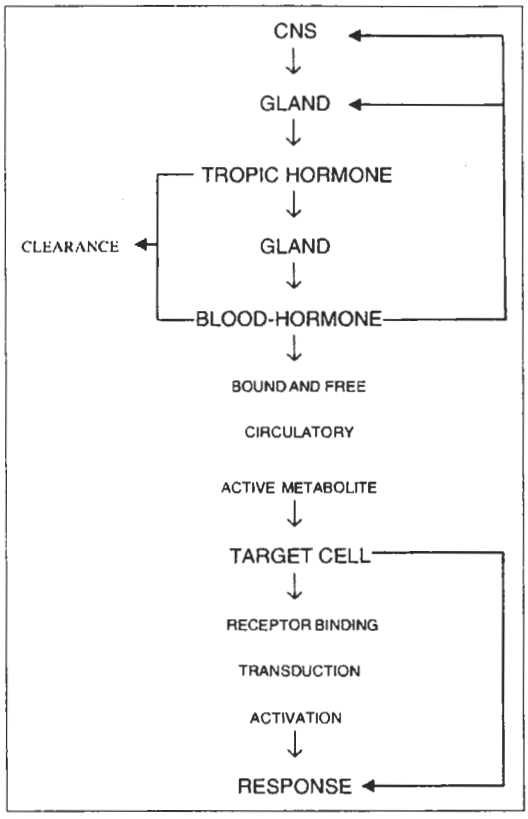

FIGURE 1 Diagrammatic representation of a typical sequence of hormone action and regulation. *Abbreviation*: CNS, central nervous system.

- Secretory and clearance rates often decrease, although it is not clear in these cases whether the primary defect involves hormone secretion or hormone clearance. The pertinent question is to what extent the capacity to maintain stable levels of plasma hormones is preserved. To better understand at which levels defects may be occurring, it is important to study hormonal biosynthetic precursors, their enzymes, and intermediary metabolites.
- Receptors located on target cells mediate specific actions of hormones on particular cells and the number of receptors may increase (upregulation) or decrease (downregulation) depending on the stimulus. Hormone-receptor complexes are usually internalized by endocytosis, bind to the nucleus, and stimulate or repress the transcription of selected RNAs or the activity of specific enzymes. Cellular responses are determined by the genetic programming of the particular cell. With aging, receptor binding and intra-cellular responses vary greatly depending on the hormone and the target cell.

■ THE ADRENAL CORTEX

The adrenals are paired glands that lie above the kidneys (Fig. 2). They have an inner medulla and an outer cortex (Fig. 3). The medulla is considered a sympathetic ganglion and it secretes the catecholamines [epinephrine (E) and norepinephrine (NE)], which are amines derived from the amino acid tyrosine. The cortex secretes several steroid compounds, characterized chemically by a 17-carbon ring system. The following are derivatives of cholesterol and share the same steroid structure: sterols, bile acids, vitamin D, and hormones from the ovary (e.g., estrogens), the testis (e.g., testosterone), and from the adrenal cortex (corticoids). Corticoids are distinguished into three categories:

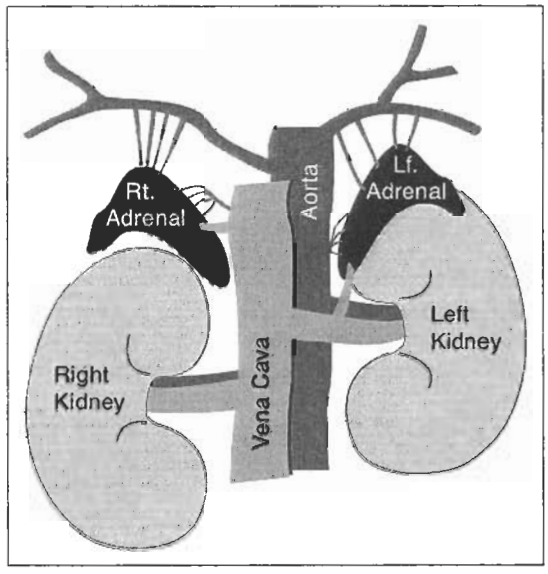

FIGURE 2 Diagram of the kidneys and adrenals.

- *Glucocorticoids*: In this group, cortisol is the principal glucocorticoid secreted in humans, and corticosterone is the principal glucocorticoid secreted in rats (Fig. 3).
- *Sex hormones*: Dehydroepiandrosterone (DHEA) is the principal adrenal androgen in humans. Cortisol and DHEA are secreted by the cells of the zona fasciculata and zona reticularis, and corticosterone is secreted by these and also the zona glomerulosa.
- *Mineralocorticoids*: Secreted by the cells of the zona glomerulosa, aldosterone is the principal hormone of this group.

The HPA axis is the most important system to guarantee adaptation and survival of an organism upon exposure to stress (Table 2). Given the complex interrelationships among the hypothalamus, anterior pituitary, and adrenal cortex, it is necessary, in evaluating the function of each component, to consider the entire axis as one entity (Fig. 4). Secretion of the adrenocorticotropin or adrenocorticotropic hormone (ACTH)

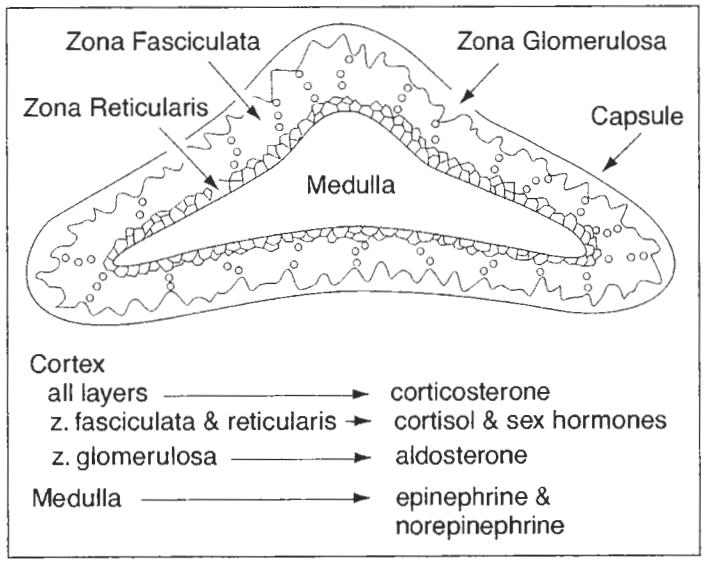

FIGURE 3 Diagram of a section of the adrenal grand illustrating the various zones and hormones.

TABLE 2 Some Characteristics of Stress

Stress induces defense mechanisms for maintenance of homeostasis in response to challenges
Some types of stress known to stimulate the HPA axis
Physical stress
Hypoglycemia
Trauma
Exposure to extreme temperatures
Infections
Heavy exercise
Psychological stress
Acute anxiety
Chronic anxiety
Anticipation of stressful situations
Novel situations
Consequences of exposure to stress
Specific responses (varying with the type of stimulus)
Nonspecific responses (always the same, regardless of the stimulus and mediated through stimulation of neural, endocrine, and immune axes)

Abbreviation: HPA axis, hypothalamo-pituitary-adrenal axis.

from the anterior pituitary is stimulated by the action of the hypothalamic corticotropin-releasing hormone (CRH). In turn, ACTH causes the release of cortisol (with a half-life in plasma of 60 to 90 minutes and a proportion in plasma of approximately 10% free and 90% bound to plasma proteins). The effects of old age on the HPA axis have been studied extensively given its importance in the maintenance of homeostasis.

■ Changes with Aging in Adrenocortical Hormones Under Basal and Stress Conditions

With aging, the adrenal cortex undergoes some structural changes. For instance, its weight is decreased in humans, and in the various animal species that have been examined, nodules (i.e., localized hyperplastic changes, perhaps reactive to a reduced blood supply or consequence of multifocal adenomas) occur frequently. The adrenocortical cells, which are typical secretory cells rich in mitochondria and endoplasmic reticulum with numerous lipid droplets where the steroid hormones are stored, undergo several changes. Of these, the most widespread is the accumulation of lipofuscin granules (Chapters 3 and 6), ultrastructural changes in mitochondria, and the thickening of the connective support tissue (as shown by the thick capsule and the fibrous infiltrations around blood vessels). Major actions of glucocorticoids are described below and in Figure 5. DHEA, the principal adrenocortical sex hormone, has weak androgenic (masculinizing) and anabolic (protein building) actions, and mineralocorticoids, such as aldosterone, regulate primarily water and electrolyte metabolism through their action on the renal tubule (Chapter 18).

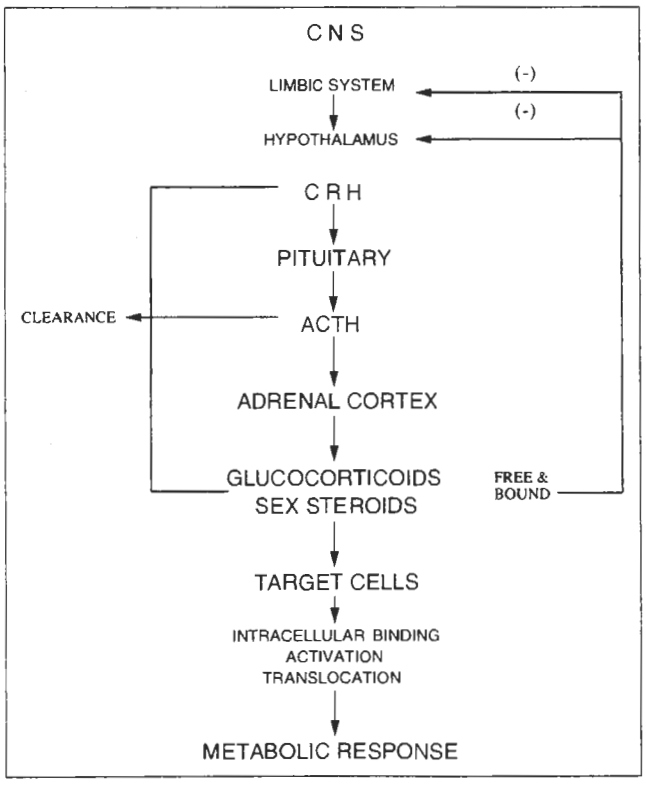

FIGURE 4 Diagrammatic representation of the HPA axis. *Abbreviations*: ACTH, adrenocorticotropic hormone; CNS, central nervous system; CRH, corticotropin-releasing hormone; HPA, hypothalamo-pituitary-adrenocortical axis.

Glucocorticoids

Under basal conditions, the following parameters remain essentially unchanged in men and women well into old age (10–12):

- Plasma levels of cortisol and ACTH
- Circadian rhythm of ACTH release
- Cortisol release
- Responses of ACTH and cortisol to administered CRH

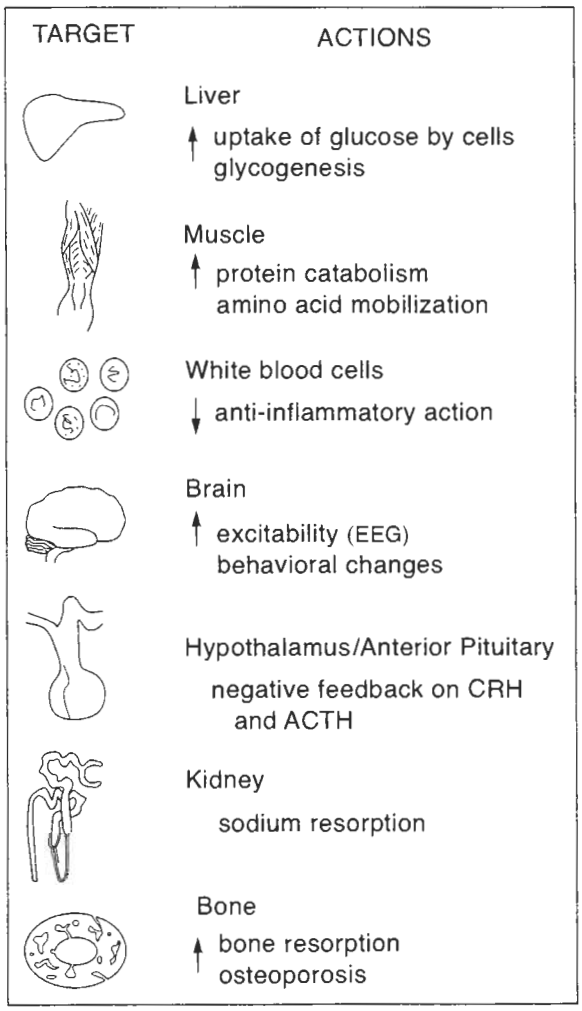

FIGURE 5 Diagram of the major actions of glucocorticoid hormones. *Abbreviations*: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; EEG, electroencephalogram.

- Number of glucocorticoid receptors in target cells or affinity of these receptors for cortisol

A number of early studies suggested that secretion of cortisol is reduced in old age. However, the reduction of corticoid secretion be compensated for by a decreased clearance (i.e., reduced metabolism and excretion), or increased hormone production may be compensated for by an increased removal (clearance). Such metabolic compensatory mechanisms could remain operative into old age, with the body adapting to decreasing production rates of the hormone by reducing the rate of its removal or vice versa and, thus, maintaining normal circulating levels. However, more recent studies indicate that the production and clearance of cortisol are unchanged if the elderly subjects are in good health (12). Yet other studies have reported that in some species [e.g., rats (13), vervet monkeys (14), tree shrews (15), baboons (16)], glucocorticoid levels are slightly increased with senescence.

Stress stimulates the entire HPA axis, resulting in increased synthesis and secretion of CRH, ACTH, and glucocorticoids. Stress also stimulates the sympathetic nervous system and the adrenal medulla to increase E and NE secretion. In some animal species, under conditions of stress (physical or psychological) or after injection of exogenous glucocorticoids, the levels of glucocorticoids are more highly elevated in the older animals. This is the case for injections of corticosterone, which not only cause corticosterone levels to increase above those of controls of the same age, but also cause the higher levels to persist for longer periods in older rats (of some strains) (Fig. 6). These persistently higher corticosterone levels after stress or after administration of exogenous corticosterone have been interpreted as a loss of resiliency of the HPA axis. That is, it is thought that the HPA axis fails to set into action the negative feedback necessary for returning the elevated hormone blood concentrations to basal levels (Box 2) (13–17).

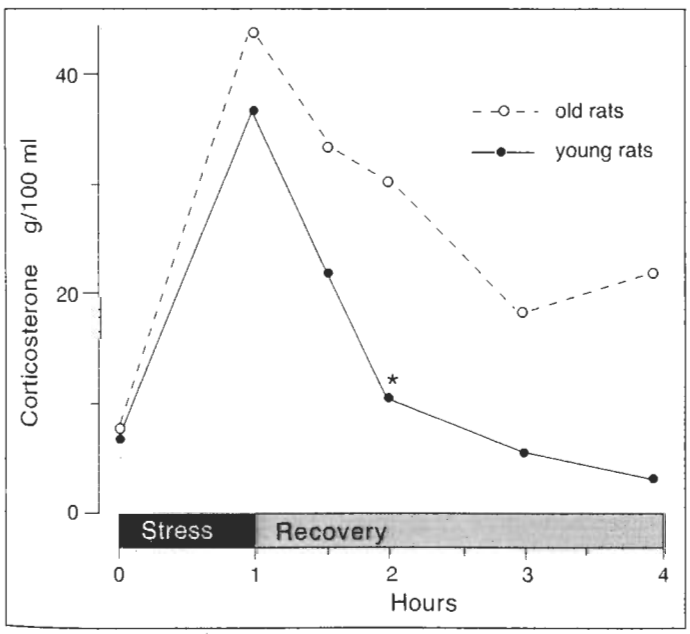

FIGURE 6 Corticosterone levels in young (three to five months) and old (24–28 months) Fisher 344 rats during one hour of immobilization stress followed by four hours of post-stress recovery. Corticosterone levels were higher and persisted higher in the old compared to the young subjects. *Indicates the times when levels are no longer significantly elevated above base line (determined by two-tailed paired *t*-test). In the case of young rats, this was one hour after the recovery period; for aged rats, such recovery did not occur during the monitored time period. *Source*: From Ref. 17.

In the rat, high glucocorticoid levels are toxic to neurons, particularly those of the hippocampus in which there is a high concentration of glucocorticoid receptors (18). Hippocampal cells under basal conditions inhibit CRH release. Therefore, when some of these cells are lost due to the toxic action of high corticosterone levels, CRH inhibition is also lost. Consequently, secretion of ACTH and glucocorticoids is increased and the levels of corticosterone in the blood continue to increase, thereby generating the "glucocorticoid cascade hypothesis of aging" (13). Young rats stressed for several weeks or treated with high glucocorticoid doses show hippocampal cell loss and changes in HPA axis function resembling those in old, stressed animals (13,17–20). In healthy humans, the relationship among the three components of the HPA axis do not appear to change significantly after long exposure to stress or with increasing age (21).

In contrast to levels of glucocorticoids that remain steady under basal conditions and rise under stress conditions, levels of the other adrenocortical steroids appear to decline with aging. This is the case for aldosterone in which values are almost undetectable beyond the age of 65 years (22). For DHEA, values for those aged 60 and older are approximately one-third of those for individuals around age 30 (23,24).

Adrenal Sex Steroids and DHEA Replacement Therapy

DHEA, the principal adrenal androgen, is considered a prototype of the adrenal sex hormones. DHEA follows a characteristic life cycle in which levels are

- very high in the fetus,
- low in childhood,
- rising before puberty,
- high in the adult, and
- progressively declining to low or negligible levels by the age of 70 years.

DHEA secretion is regulated by ACTH. Under conditions of stress, the secretion of cortisol and DHEA is increased, but the ratio of DHEA to cortisol falls as the enzymatic pathways for the biosynthesis of both hormones use the same intermediates, with preferential formation of cortisol (23,24). The reduced plasma levels together with the lower response of DHEA to ACTH administration have led to the suggestion that DHEA may have some antiaging effects, perhaps attributable to an antiglucocorticoid action. For example, severely atherosclerotic individuals have lower DHEA levels compared to normal individuals (25–27). This and other evidence have led to the claim that DHEA replacement may prevent some of the functional decrements and pathology of old age. It may be recalled that the physiologist C.-E. Brown-Séquard, by early 1889, recognized an association between aging and secretory actions attributed to an organ (the testis), and he extolled the antiaging properties of testicular secretions (androgens) (28). Testicular transplants and administration of androgens have been used repeatedly as possible rejuvenating measures to delay or reverse aging, but these attempts have met with little success. Indeed, high levels of androgens in aging men may even aggravate the incidence and severity of prostate hypertrophy and cancer (Chapter 18).

Effects of DHEA replacement therapy have been examined in animals. Long-term DHEA administration in old mice has reduced the incidence of mammary cancer, has increased survival, and has delayed the onset of immune dysfunction (29). DHEA administration also leads, in animals, to decreased

BOX 2 *Feedback Mechanisms Applicable to Hypothalamo-Pituitary-Endocrine Axes and the Portal Pituitary Blood Vessels*

Hypothalamo-pituitary-endocrine axes use feedback signals to regulate their secretory activity around a *set-point value* necessary for homeostasis. The set-point is maintained by negative feedbacks operating in a manner similar to an engineering control system with a set-point, a controlling element, a variable element, an integrator, and a feedback signal.

In almost all physiologic systems, if a discrepancy arises between the set-point and the variable element, an error signal is delivered to the controlling element to produce an adjustment in the direction opposite to the original deviation from the set-point. This type of control system, in which a variable provides a signal for compensatory reduction in the value of the variable, is referred to as a *negative feedback mechanism.* In the case of the hypothalamo-pituitary-adrenal axis, corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoid secretions are inter-regulated by feedbacks operating at each level. *Low blood glucocorticoid levels increase CRH secretion and CRH stimulates ACTH release, which, in turn, stimulates adrenal cortex glucocorticoid secretion. High levels of blood glucocorticoid levels inhibit CRH and ACTH secretion and, consequently, decrease adrenal glucocorticoid secretion. In each case, the needed result is the return of glucocorticoid levels to the original "set-point" level.*

Signals are relayed from one component of the axis to the other and from the periphery to the axis by short- and long-term loops. The short-term-loop feedback signals are carried through the portal blood vessels from the hypothalamus to the pituitary and vice versa (by retrograde flow). In the long-term loop, feedback signals are relayed from the peripheral endocrine gland and the target tissues to the pituitary and the hypothalamus through the general blood circulation.

Portal pituitary vessels represent a direct vascular link between the hypothalamus and the anterior pituitary. On the ventral surface of the hypothalamus, capillary loops from the carotid arteries and the circle of Willis form a vascular plexus that carries blood down the pituitary stalk to the capillaries of the anterior pituitary. This arrangement constitutes *a blood portal system beginning and ending in capillaries without going through the heart and general circulation.* Hypothalamic hypophysiotropic hormones are carried without dilution in the peripheral blood, directly to the anterior pituitary where they stimulate synthesis and release of the pituitary hormones.

food intake and body weight loss. This suggests that, despite its minor anabolic activity, DHEA may act in a manner similar to caloric restriction in extending the life span and in retarding tumorigenesis and immunosenescence (30–32) (Chapter 23).

Mineralocorticoids

Secretion, blood levels, and clearance rates of aldosterone decrease in the elderly (22). This decrease has been attributed to a declining adrenergic receptor activity (33); yet, the persistence of normal plasma electrolyte balance despite lower aldosterone levels demonstrates the efficiency of compensatory mechanisms even in old age (22). Impaired conservation of urinary sodium, which may occur in old age (Chapter 18), has been attributed to defects in the renin-angiotensin-aldosterone axis (34). While renin concentrations remain stable or decline with advancing age, plasma aldosterone levels decline. Reduced aldosterone levels have been attributed not only to the decrease in renin (when renin declines do occur) (35), but also to the reduced activity of biosynthetic enzymes for the hormone (as well as to the reduced number of calcium channels) (35,36).

Adrenal Steroid Receptors

The classical view of the mechanism of action of adrenal steroids is that adrenal steroids exert their cellular and molecular actions by binding to cytoplasmic (cytosolic) and nuclear receptors and that the degree of cellular responsiveness is directly proportional to the number of occupied receptors. The hormone-receptor complexes are then translocated to nuclear receptor sites in the nucleus where they modify gene expression (Fig. 7). The ensuing action occurs with a lag time lasting hours or days. It is now recognized that hormone-receptor responses are mediated, in addition to genomic mechanisms, by nongenomic mechanisms. Nongenomic mechanisms are characterized by rapid-onset actions that are mediated through binding of the hormone to membrane receptors, which, in turn, activate second messengers and various signal transduction cascades (37).

Adrenocortical steroid receptors are members of the steroid hormone/nuclear receptor family comprised of the vitamin D receptor, retinoid receptor, and thyroid hormone receptor, as well as a number of so-called "orphan" receptors (because their ligand and function are not well identified) (38–40). All classical steroid receptors (androgen, AR; estrogen, ER; glucocorticoid, GR; mineralocorticoid, MR; and progesterone, PR) are phosphoproteins that, in the absence of the activating signal, are

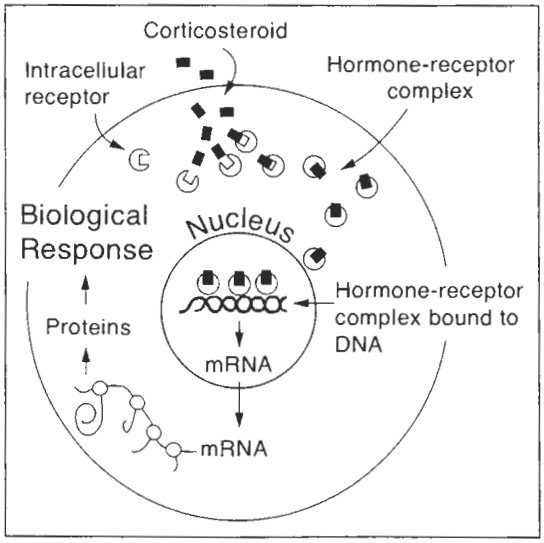

FIGURE 7 Schematic diagram of corticosteroid action in a target cell.

associated with heat shock proteins (HSPs) (41). They all act as transcriptional regulatory proteins and are able to interact with select target genes (40–42).

Numerous mechanisms account for this selectivity, such as interaction with DNA-bound transcription factors, the presence of chaperones, phosphorylation, and subnuclear trafficking pathways that facilitate receptor scanning of the genome (37–43). Several steroid receptors can be activated in the absence of the hormone. This is the case of ERs that bind competitively to antagonist or agonist nonsteroidal molecules (i.e., selective estrogen receptor modulators, Chapter 10), but this does not seem to be the case for glucocorticoids (43) despite data on the binding of the antagonist RU486 (44). The finding that some of the receptors may be activated by signal transduction pathways in the absence of the specific hormone, although not immediately applicable to adrenocortical receptors, may be worth pursuing in future studies considering the current progress in our understanding of the role of coactivators and corepressors in modulating action of estrogen and progesterone receptors (44,45).

All molecular events in the hormone-cellular response pathway subsequent to receptor binding are subject to alteration with age, although the nature and magnitude of these age-related changes are variable depending on the hormone, the target cell, and the animal species. Overall, the concentration of corticosteroid receptors decreases either in early adulthood or during senescence (46). For example, in the rat brain, glucocorticoid receptors are detectable on day 17 of gestation, the receptors increase gradually after birth to adult levels by 15 days of postnatal age, but then are significantly reduced in aged animals (24-months-old) (47). The concentration of cytosolic corticosterone receptors in the primary glucocorticoid-concentrating region of the brain, the hippocampus, decreases with aging, with no change in receptor affinity or capacity for nuclear translocation (47). Some of the receptor physicochemical properties (e.g., activation, transformation) seem to be more susceptible to aging than the number of receptors. Such age-related changes have been reported in glucocorticoid receptors in liver, in skeletal muscle, and in the cerebral hemisphere. Aging changes in corticosteroid receptors that alter the responsiveness of target cells and molecules to hormones may contribute to the decline in the effectiveness of adrenocortical responses to stress.

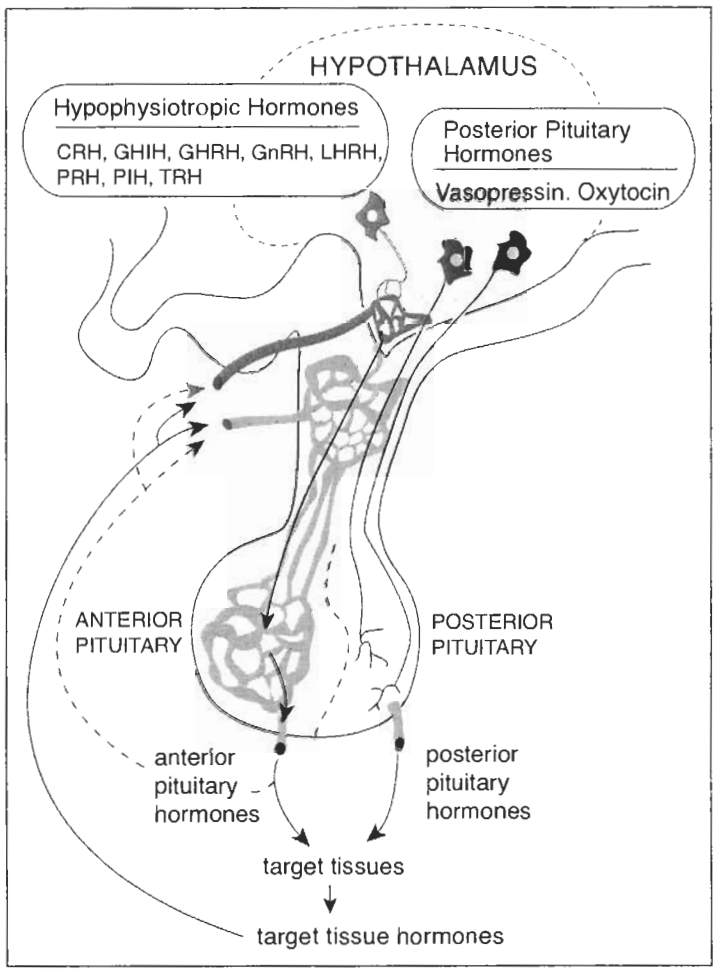

FIGURE 8 Diagram of the relationships among hypothalamus, pituitary, and target tissues. The neuroendocrine cells of the hypothalamus secrete both (1) hypophysiotropic hormones that are carried by a local portal system directly to the anterior pituitary where they stimulate the synthesis and release of anterior pituitary hormones, and (2) hormones that are carried to the posterior pituitary and released from there into the general circulation. Major hypophysiotropic hormones include GnRH, CRH, GHRH, GHIH or somatostatin, PRH, PIH, and TRH. The hypothalamic hormones that are carried to the posterior pituitary include ADH or vasopressin and oxytocin. The arrows indicate the presence of regulatory feedbacks between the circulating levels of the hormones and their release from the hypothalamic neuroendocrine cells. *Abbreviation*: CRH, corticotropin-releasing hormone; GHIH, growth hormone-inhibiting hormone; GHRH, growth hormone-releasing hormone; PIH, prolactin-inhibiting hormone; PRH, prolactin-releasing hormone; TRH, thyrotropin-releasing hormone; ADH, antidiuretic hormone; GnRH, gonadotropins releasing hormones.

■ Regulation of Adrenocortical Secretion

As illustrated in Figure 8, circulating levels of adrenocortical hormones depend on a hierarchy of regulation, from the hypothalamus to the pituitary, to the adrenal gland (Box 2) and, ultimately, to the target tissues, cells, and molecules. With aging and under conditions of stress, a disruption of this complex regulatory system at one or more levels may result in failure of homeostasis and adaptation.

CRH, a polypeptide released from neurons in the median eminence of the hypothalamus, is transported via the portal system to the corticotropes of the anterior pituitary, where CRH stimulates synthesis and release of the ACTH. ACTH, a protein released from the anterior pituitary, stimulates cells of the two inner zones of the adrenal cortex to synthesize and release the glucocorticoids and sex hormones (Fig. 3). Thus, after ablation of the pituitary, these two zones atrophy, and the circulating levels of the corresponding hormones decrease. Conversely, in tumors of the pituitary in which ACTH levels are increased (as may occur in Cushing's disease), the two adrenocortical zones hypertrophy, and the hormonal levels increase (48).

ACTH is secreted in bursts throughout the 24-hour day, with the pulses being most frequent in the early morning and least frequent in the evening. The resulting circadian (diurnal) rhythm in cortisol secretion is largely preserved during aging in humans, but there may be a modest flattening and shift of the diurnal rhythm. Regardless, sustained nighttime cortisol levels (i.e., a reduced nocturnal drop in cortisol levels compared with daytime values) have been correlated with (*i*) reduced renal clearance of the hormone (Chapter 18), (*ii*) reduced muscle mass and generally reduced basal metabolism (Chapter 24), and (*iii*) alterations in sleep patterns and insomnia (Chapter 7).

In addition to ACTH, the adrenal cortex is stimulated to secrete glucocorticoids by the action of the antidiuretic hormone (ADH), one of the two hormones of the posterior pituitary. The major action of ADH is to stimulate retention of water by the kidney in which urine becomes concentrated and its volume

decreases (Chapter 18). Other functions of ADH include elevation of arterial blood pressure (hence the alternative name of vasopressin) and maintenance of blood homeostasis. ADH also has some metabolic actions and causes glycogenolysis in the liver. In relation to the *adrenal cortex, ADH increases ACTH secretion by stimulation of the corticotropes (pituitary cells secreting corticosteroids).* Lastly, a variety of stimuli increase ADH secretion, such as pain, nausea, stress, some emotions, and some drugs.

■ THE ADRENAL MEDULLA

The adrenal medulla is part of the sympathetic division of the autonomic nervous system, and, as such, it functions in unison with the other sympathetic structures. The main secretions of the adrenal medulla are E, NE, and, to a lesser extent, dopamine (DA) (Fig. 3). These chemicals are derived from the amino acid tyrosine and are chemically classified as catecholamines. NE also acts as a neurotransmitter in the central nervous system (CNS).

The adrenal medulla is interrelated anatomically and functionally with the adrenal cortex by a rich vascular network in which blood flowing from the cortex to the medulla provides high concentrations of glucocorticoids which induce in the medulla some of the enzymes for catecholamine synthesis [e.g., the enzyme phenylethanolamine-*N*-methyltransferase (PNMT)]. NE is formed by hydroxylation and decarboxylation of thyrosine, and E is formed by methylation of NE by the enzyme PNMT. In addition, glucocorticoids have some metabolic interaction with medullary hormones (e.g., mobilization of free fatty acids in emergency situations). Major actions of the catecholamines are summarized in Figure 9, and mechanisms of cellular stimulation are summarized in Figure 10. The catecholamines, like other transmitters, are released at the synaptic cleft where their actions are terminated by three mechanisms: (*i*) they bind to the postsynaptic receptors to stimulate the target cell; (*ii*) they bind to presynaptic receptors for reuptake into the presynaptic cell; and (*iii*) they are metabolized by the enzymes monoamine oxidase and catechol-*O*-methyltransferase (Chapter 6, Fig. 6.11). Thus, the efficiency of neurotransmission depends on both the release and the removal of the chemical transmitter at the synapse.

The autonomic nervous system is comprised of sympathetic and parasympathetic divisions, and its dysfunction is a well recognized, although poorly understood, consequence of old age. One of the anatomical characteristics of the autonomic sympathetic division is its organization into a paravertebral sympathetic ganglion chain that, under emergency conditions of stress, can discharge as a unit, as in "rage and fright," when sympathetically innervated structures are stimulated simultaneously over the entire body (Fig. 11). This emergency response causes heart rate to accelerate, blood pressure to increase, bronchioles and pupils to dilate, and many other changes (Table 3). *The contribution of the adrenal medulla to "the emergency function" of the sympatho-adrenal system involves the perception of stress and functional responses to it.* Although the adrenal medulla is not essential for life under nonstress conditions, as its absence may be relatively well compensated for by activation of other sympathetic neurons, it is indispensable under stress conditions.

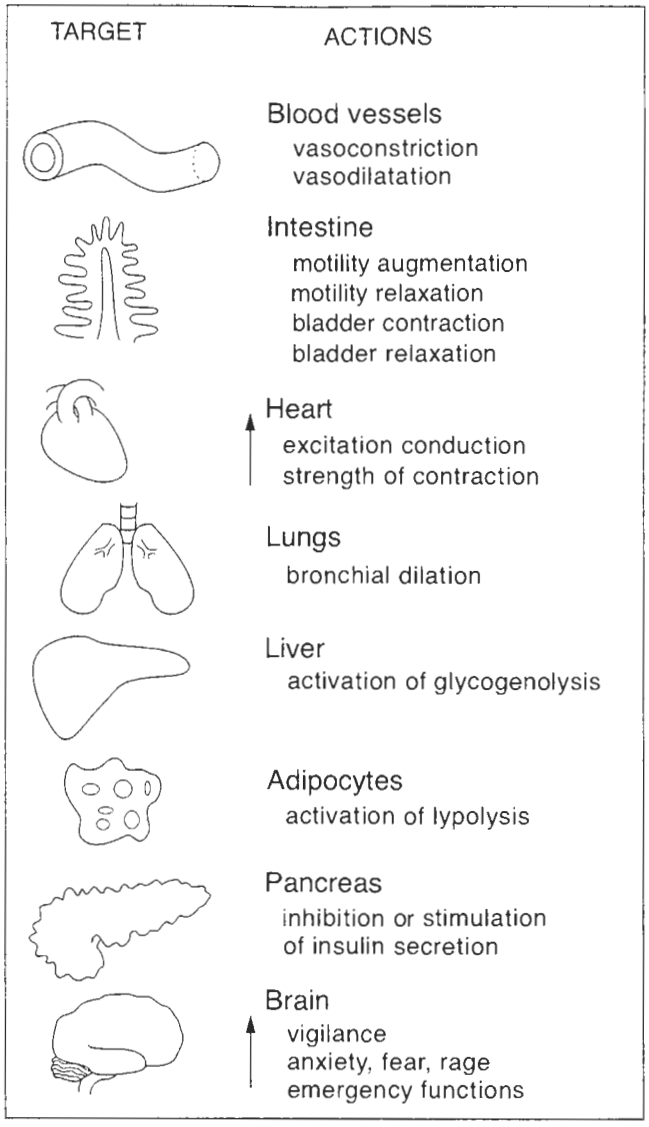

FIGURE 9 Major actions of adrenal catecholamines, E and NE. Both E and NE act on α and β receptors, with NE having a greater affinity for α-adrenergic receptors and E- for β-adrenergic receptors. *Abbreviations*: E, epinephrine; NE, norepinephrine.

■ Variability of Changes with Aging

The structure and function of autonomic neurons appear to be altered with aging. Major structural changes include swelling of axonal neurons with neurofilament aggregates, accumulation of lipofuscin, and decreased catecholamine fluorescence. These structural changes are associated with dysfunction of body temperature, bowel motility, cardiovascular maintenance (also partly regulated by parasympathetic inputs), blood pressure, water and electrolyte distribution, and energy metabolism. Several studies indicate that basal sympathetic activity increases in some elderly individuals, and the increase may be associated with dysregulation of the ability of the sympathetic nervous system to respond to a variety of challenges (49,50). Under basal conditions, in humans, plasma levels and urinary excretion of E and NE are highly variable. With aging, these hormones may do the following:

- Remain unchanged
- Show a reduction in absolute and average circadian amplitude
- Show an increase, with the increase being greater after standing and physical exercise

Elevation of plasma and urinary catecholamines, reported after a variety of stimuli, has been interpreted as a compensatory reaction to the apparently increasing refractoriness with

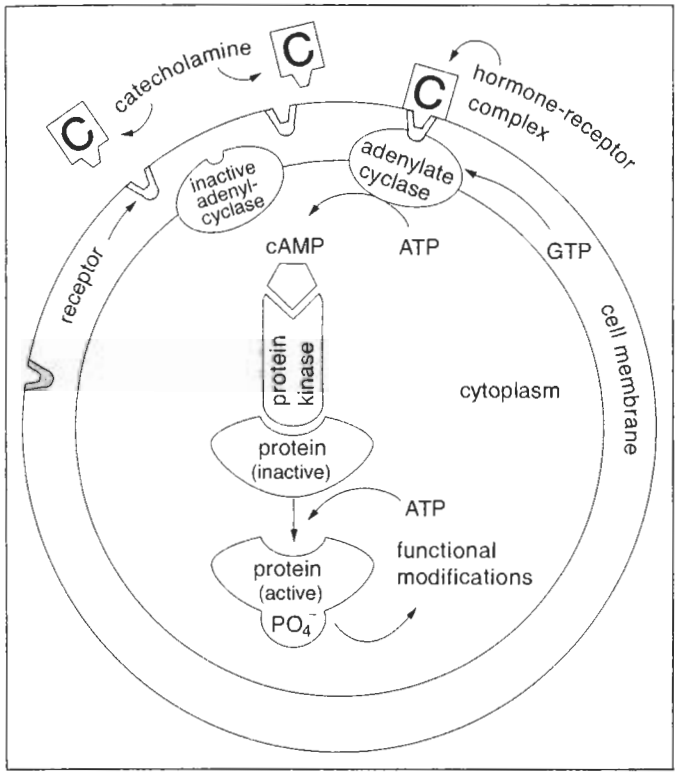

FIGURE 10 Schematic diagram of the action of catecholamines, E and NE, in a target cell. *Abbreviations*: E, epinephrine; NE, norepinephrine; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GTP, guanosine triphosphate; PO_4.

aging (perhaps due to receptor downregulation) of target tissues to catecholamines (33,49–52). However, the apparent increase in NE plasma levels does not occur with all stimuli, and, additionally, the time it takes to return to baseline levels is prolonged in the elderly. Also, NE and E often show differential responses. For example, in an elderly subject during a mental stress test, plasma NE might be elevated, whereas plasma E might stay stable. Given the wide distribution of NE throughout the sympathetic nervous system and CNS, in contrast to the circumscribed localization of E in the medulla, the differential response of NE and E suggests hyperactivity of the sympathetic system in general, rather than that of the adrenal medulla in particular.

■ Target Differential Responsiveness

In the elderly, high levels of catecholamines may be due to either a higher release from the adrenal medulla or a reduction in peripheral clearance. *One proposed explanation for the overall increase of sympatho-adrenal activity with aging is an increased refractoriness (or decreased sensitivity) of target tissues to catecholamines due to alterations in transport and binding, and, therefore, the need for enhanced NE and E secretion.* A decrease in the number of adrenergic receptors with aging has been reported in some organs and cells (e.g., cerebellum, adipocytes) and a decrease in receptor affinity has been reported in others (e.g., lung), but in many cases, changes are not observed. Although current findings do not support the view that the number of receptors decreases with aging, several concomitant factors (e.g., aging-associated decrease in cell membrane fluidity) may mask true declines.

NE and E both act on α and β receptors, but NE has a greater affinity for α adrenergic receptors, whereas E has a greater affinity for β adrenergic receptors. Both α and β receptors are G protein receptors that span the cell membrane; G proteins are nucleotides, regulatory proteins that bind to GTP (guanosine triphosphate protein) (Fig. 10). Clinical and experimental observations have been conducted primarily of β1 receptors and the other β2 and α adrenergic receptors. An important finding is that the responsiveness of the receptors to adrenergic stimulation depends on the type of tissue in which the receptors are located (47,51,52). Decreased responsiveness may be found in the diminished efficiency of hemodynamic and cardiovascular responses to changes in posture (Chapter 7) and the slower dark adaptation of pupil size (Chapter 8). In contrast, increased responsiveness occurs in those organs and tissues regulating blood pressure. It is worthwhile to recall here that the loss of dopaminergic neurons in the cerebral basal ganglia is a major cause of Parkinson's disease (Chapter 6). Other hormones, such as thyroid hormones, that are known to affect catecholamine metabolism, may also increase the effects of catecholamines on blood pressure (Chapter 12).

■ THE PITUITARY GLAND

The pituitary gland (also called the hypophysis) regulates, through the secretion of its tropic hormones, the activity of several peripheral endocrine organs (adrenal cortex, thyroid, gonads) and other target tissues (e.g., bones, muscles). In humans, the pituitary gland is divided into two lobes, anterior and posterior. A third part, between the two, the intermediate lobe, is structurally and functionally rudimentary in humans. Together with cells dispersed in the anterior lobe, the intermediate lobe secretes melanotropin, which is related to skin and hair pigmentation (Chapter 21) and γ lipotropin, whose function is still little known.

The pituitary has close functional ties with the hypothalamus and, indirectly, other CNS centers, especially the limbic system. *The hypothalamus produces a number of peptides, the hypophysiotropic hormones, that are carried directly to the anterior pituitary by a local portal system (Fig. 8). The hypophysiotropic hormones stimulate or inhibit the synthesis and release of the anterior pituitary hormones.* Hormones of the anterior pituitary and their major functions are listed in Figure 12. The hypothalamic neuroendocrine cells secrete two peptide hormones that are carried by axonal flow to the posterior pituitary where they are stored until they are released into the circulation. Hormones of the posterior pituitary and their major actions are illustrated in Figure 13. *The hypothalamus is also involved in the regulation of the autonomic nervous system and of a number of behaviors (e.g., sex, fear, rage) (53,54).*

■ Structural Changes

The pituitary gland changes little with aging. Although changes have been described, it is still unclear if these changes involve the gland globally or involve localized parts of the gland.

In the anterior lobe, changes with aging are relatively few and include cellular changes typical of aging cells (e.g., accumulation of lipofuscin). Tumor incidence, primarily prolactinomas [tumors secreting prolactin (PRL)], increases with aging in rats and mice, and more so female. In the posterior lobe, studies in old rodents reveal a number of changes, such as decreased size and number of neurosecretory granules, reduced number of hormone receptors, increased autophagic activity, increased perivascular space, decline in cell volume, and

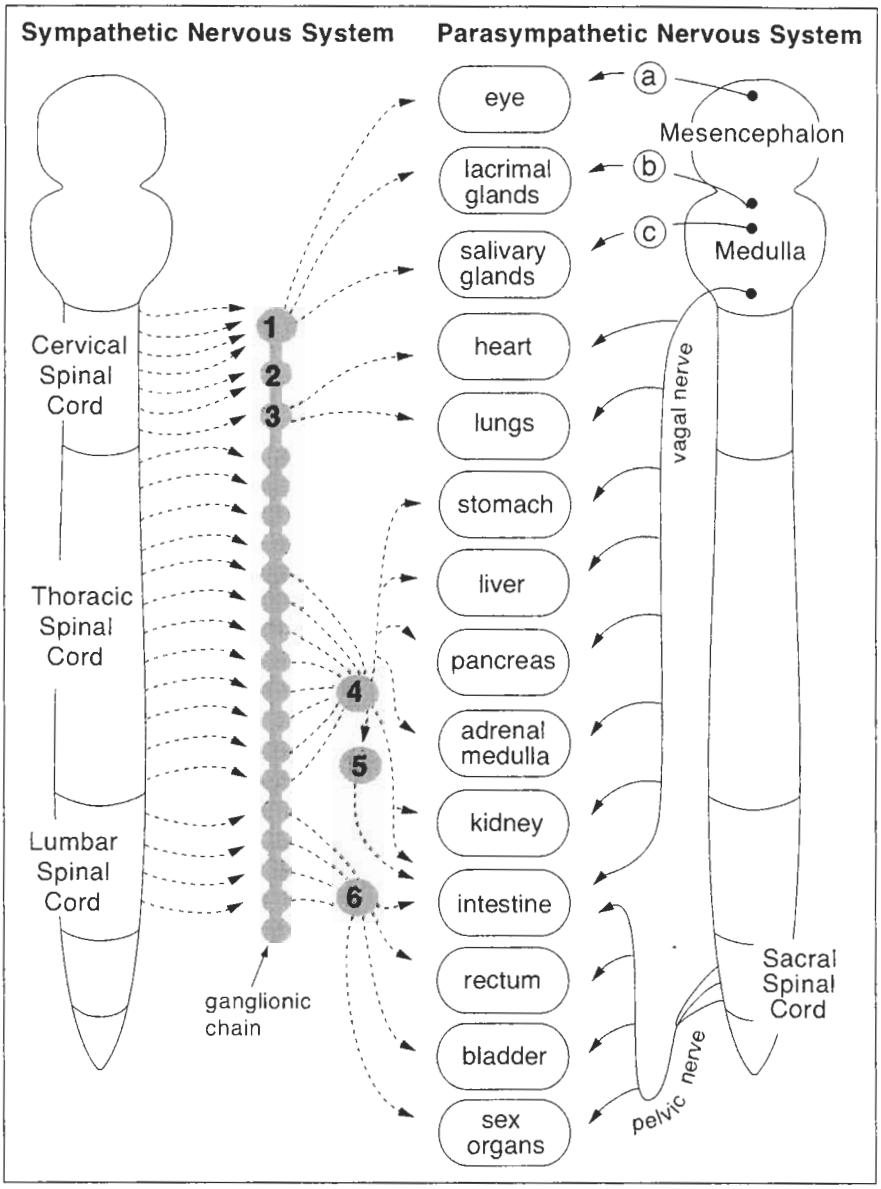

FIGURE 11 Diagram of the efferent pathways of the autonomic nervous system. The two systems, the sympathetic and the parasympathetic, often act antagonistically: for example, sympathetic stimulation usually accelerates the speed of cardiac contraction and increases blood pressure, whereas parasympathetic stimulation decreases both of them. Stimuli from the sympathetic neurons, located in the lateral columns of the spinal cord, are relayed to the paravertebral sympathetic ganglion chain and from the ganglia to the peripheral viscera. In the case of stress, they are activated simultaneously and generate those multiple responses necessary for survival and adaptation. Other sympathetic neurons include the (1) superior, (2) middle, (3) inferior, cervical ganglia (4), celiac ganglion (5), superior mesenteric ganglion (6), inferior mesenteric ganglion. The parasympathetic neurons are located proximal to the organs they innervate and stimulate them individually. They include the cranial ganglia that supply the visceral structures in the head through the (a) III, (b) VII, and (c) IX cranial nerves, and to the organs of the thorax and upper abdomen by the X cranial nerve (vagus). The pelvic nerve originates in the sacral spinal cord and supplies the lower abdomen viscera and the sex organs.

reduction in endoplasmic reticulum activity. In humans and other examined animals (e.g., cattle), such changes are rare.

■ Growth Hormone, Growth Hormone–Releasing Hormone, and Somatostatin

Aging is associated with a decrease in protein synthesis of lean body mass and bone formation as well as with an increase in adiposity (fat). This association suggests the involvement of growth hormone (GH) because of its anabolic (i.e., protein synthesis promoting) and metabolic actions (Box 3). Although some studies have reported a decrease in basal levels of GH, the number of somatotropes (i.e., pituitary cells secreting GH), the pituitary content of GH, the basal plasma levels of the hormone, and its clearance remain essentially unchanged into old age.

Obesity lowers circulating GH levels in young individuals, and the presence of obesity in some elderly may contribute to the decreased GH levels. Contradictory changes in GH levels have been reported in the elderly after exposure to stimuli known to cause GH release. In rats, GH elevation after stimulation by a variety of means is less marked in old animals, and, consistent with those findings, in humans after stress, surgical trauma, exercise, and arginine stimulation, the expected increase of GH secretion is often considerably blunted or even entirely lacking (55).

TABLE 3 "Fright, Flight, or Fight" Responses to Stress

Increased blood pressure
Increased heart rate
Increased force of heart contraction
Increased heart conduction velocity
Shift of blood flow distribution away from the skin and splanchnic regions and more to the heart, skeletal muscle, and the brain
Contraction of spleen capsule (increased hematocrit i.e., increased proportion of red blood cells to whole blood volume)
Increased depth and rate of respiration
Mobilization of liver glycogen to glucose (glycogenolysis)
Mobilization of free fatty acids from adipose tissue (lipolysis)
Mydriasis (widening of pupil)
Accommodation for far vision (relaxation of ciliary muscle)
Widening of palpebral fissure (eyelids wide open)
Piloerection (erection of hair)
Inhibition of gastrointestinal motility and secretion, and contraction of sphincters (ringlike muscles closing an orifice)
Sweating (cold sweats as skin blood vessels are constricted)

GH secretion in humans undergoes a nocturnal peak during the first four hours of sleep, coinciding with stages III and IV of slow-wave sleep. These stages are the most affected in aging (Chapter 7). Studies in older persons have shown a decrease in sleep-related GH secretion and an occasional decrease in the nocturnal peak. The latter finding has been attributed to low levels of growth hormone–releasing hormone (GHRH) and high levels of somatostatin or growth hormone–inhibiting hormone (GHIH) (56). However, the exact nature of the relationship between GH levels and sleep quality over age remains controversial (and so too does the exact nature of the relationship between GH levels and body weight over age).

The effects of GH on growth and protein metabolism depend not only on GH levels, but also on the interaction between GH and somatomedins, which are polypeptide growth factors secreted by the liver and other tissues in response to stimulation by GH. The majority of growth factors act by paracrine communication, that is, they reach their neighboring cells directly without being carried by the blood to distant targets. The principal and, in adult humans, probably the only circulating somatomedins is insulin-like growth factor-1 (IGF-1). Insulin-like growth factor-2 (IGF-2), is present and active primarily during the embryonic/fetal periods. As noted in Chapter 3, suppression of IGF-1 receptors (IGF-1Rs) and, hence, suppression of the actions of this hormone, lengthens the life span in worms, flies, and mice, and has several concomitant actions such as increasing resistance to stress (Chapter 3). In humans, IGF-1 levels decrease with old age, but the functional consequences of their decrease still remain controversial.

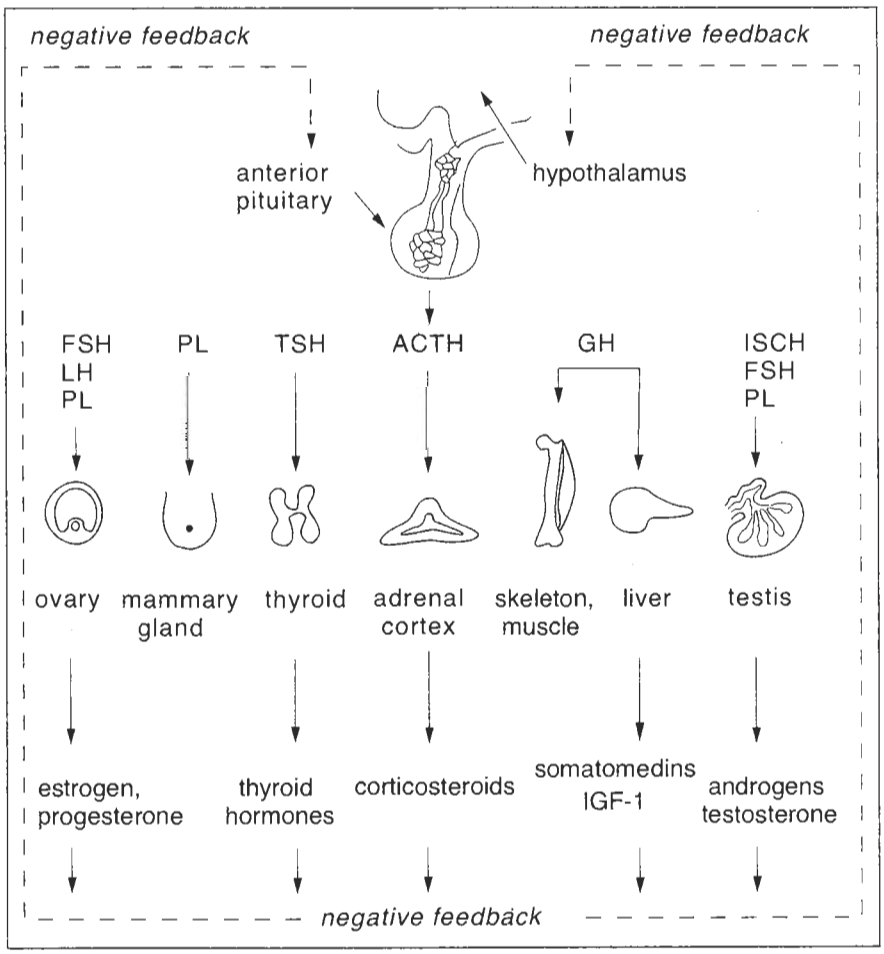

FIGURE 12 Diagrammatic representation of the major hormones of the anterior pituitary and the endocrine glands and tissues on which these hormones act. Note that the regulation of hormone levels depends on negative feedback (Box 2) except for the positive feedback of estrogens on LH secretion from the pituitary (Chapter 10). *Abbreviations*: FSH, follicle-stimulating hormone; LH, luteinizing hormone (women); ICSH, interstitial cells–stimulating hormone (men); PL, prolactin; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; GH, growth hormone; IGF-1, insulin-like growth factor-1.

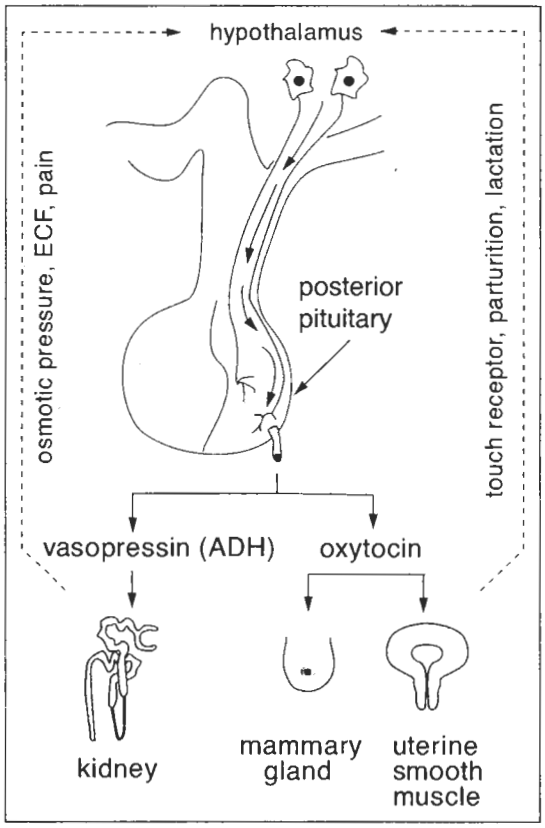

FIGURE 13 Diagrammatic representation of the major hormones of the posterior pituitary and the endocrine glands and tissues on which these hormones act. ADH and oxytocin are synthesized and secreted by the hypothalamic, supraoptic, and paraventricular nuclei; they are transported by axonal flow to the posterior pituitary, from where they are released directly in the general blood circulation. *Abbreviations*: ADH, antidiuretic hormone; ECF, extracellular fluid.

GH Replacement Therapy

Some elderly individuals have low blood levels of GH as well as low IGF-1 levels (57). In these elderly, relatively long-term administration (six months) of biosynthetic human GH increases muscle and bone mass and decreases adipose tissue. These beneficial effects are small (10–14% change) and last only as long as the hormone is administered. However, the hormone may decelerate the decline in muscle and bone with aging and consequently help to prevent the falls and bone fractures that are major causes of disability and mortality (Chapter 21) (58,59). These small and temporary observations, together with those of the potentially beneficial effects of other hormone replacement therapies (Chapters 10–13), have led to speculation about whether reduced GH and IGF-1 levels found in old age contribute to physiologic decline and increased pathology and whether GH and/or IGF-1 administration may delay aging and prolong the life span. Despite the enthusiasm about possible GH therapies, GH administration in a variety of conditions in humans (including cardiac failure, healing of burns and other wounds, and Alzheimer's disease) has been proven disappointing (60).

A number of experiments in animals testing for the possible beneficial effects of GH/IGF-1 on longevity are controversial. For example, *the levels of GH/IGF-1 in young calorie-restricted animals are reduced compared to young non–calorie restricted (i.e., fed ad libitum) animals.* In old fed ad libitum animals, there is also a reduction in GH/IGF-1 levels when compared to the young control animals. In old animals caloric restriction postpones the decline of the levels of GH/IGF-1. The persistence of relatively high levels of GH/IGF-1 in calorie-restricted old animals has been interpreted to mean that these high levels of GH/IGF-1 may mediate the beneficial effect of caloric restriction in old age and thereby help explain the animal's longevity. This latter interpretation would, then, justify the use of GH or IGF-1 administration in the elderly to delay the onset of functional impairment and

BOX 3 *The Structure and Actions of the Growth Hormone*

The growth hormone (GH) is a protein encoded by five genes on chromosome 17. GH has a high degree of species specificity, and it is bound, in plasma, to two proteins. The GH receptor is part of the cytokine receptor superfamily. Major actions of GH include:

Before adulthood

- Growth stimulation
- Increased protein anabolism
- Stimulation of insulin-like growth factor-1 (IGF-1) by tissues

In adulthood

- Stimulation of IGF-1 by tissues
- Increased lean body mass and metabolic rate
- Decreased body fat with increased plasma free fatty acids, thereby providing a ready source of energy for the tissues during hypoglycemia, fasting, and stressful stimuli
- Decreased blood cholesterol
- Increased hepatic glucose output (diabetogenic effect)
- Anti-insulin effect in muscle
- Stimulation of pancreatic B-cells, thereby making them more sensitive to insulinogenic stimuli, with resulting diabetes due to B-cell exhaustion
- Growth [GH was originally thought to produce growth by direct action on tissues (e.g., bones, muscles), but it is thought today that GH acts both directly and indirectly through the stimulation of a somatomedin, the IGF-1 (in the adult)]

GH secretion is controlled via the hypothalamus which secretes into the portal blood both growth hormone–releasing hormone, which stimulates GH secretion from the anterior pituitary, and growth hormone–inhibiting hormone, or somatostatin, which inhibits GH secretion. GH secretion is under feedback control as are the other anterior pituitary hormones. Additional factors can stimulate (e.g., hypoglycemia, fasting, stress) or inhibit (e.g., glucose, free fatty acids) GH secretion.

to prolong life. However, this view is not supported by studies in GH receptor knockout dwarf mice in which the phenotype induced by GH/IGF-1 deficiency is that of a much healthier animal with a longer survival rate.

In humans, it is well known that GH excess has detrimental effects and has been associated with acromegaly, diabetes mellitus, arthritis, and hypertension. In the interventions conducted so far in the elderly, administration of GH to individuals with low or normal GH/IGF-1 levels has resulted in increased morbidity (e.g., joint swelling and pain, cardiac arrhythmia, insulin resistance). These unwanted side effects and the possibility of increased mortality, together with the lack of solid evidence of beneficial effects, diminish the usefulness of GH treatment (60). Generally speaking, bone and muscle mass can be improved with good nutrition and physical exercise at all ages, and, therefore, these measures should be encouraged in preference to other, less efficacious and more risky interventions such as GH treatment (Chapter 24).

Somatostatin

Although the major function of GH is to promote whole-body growth (e.g., visceral organs, bones, tissues) during childhood and adolescence, GH continues to be secreted throughout life. Like GH, somatostatin also continues to be secreted throughout life and it regulates GH secretion. *In addition to inhibiting GH release, somatostatin also inhibits thyrotropin or thyroid-stimulating hormone (TSH) release. Somatostatin acts locally (by paracrine communication) and its levels in plasma are negligible. Somatostatin is secreted from the hypothalamus and other tissues (e.g., pancreas, intestine) and has multiple biologic actions (in addition to the inhibition of GH secretion). For example, somatostatin secreted in the pancreas and intestine inhibits the secretion of pancreatic and intestinal hormones.* Basal plasma levels (originating primarily from the pancreas and intestinal wall neurons) are higher in the elderly compared to young adults, but daytime variations and responses to administered meals are lower in amplitude in the elderly (61–63).

In patients with Alzheimer's and Parkinson's diseases, brain somatostatin levels are decreased in regions that also have cholinergic deficits (62) and in the cerebrospinal fluid (Chapters 6 and 7) (63). Somatostatin secretion is also influenced by neurotransmitter release and is stimulated by increased NE and DA discharge from brain catecholaminergic neurons. It is not clear whether the decline in NE and DA that occurs during aging (Chapter 6) accounts for the decrease in GH by way of a reduction in GHRH release or an increase in somatostatin release. Somatostatin-secreting or -containing tumors have equal incidence in men and women, with a peak incidence in the fifth decade of life. Half of these affected subjects also have other endocrine diseases (64).

Insulin-Like Growth Factor-1

Although not a pituitary hormone, IGF-1 is mentioned here because of its close functional relationship to GH. IGF-1 is produced locally in the brain and acts through widely distributed receptors (65). In addition to regulating of somatic growth and metabolism (along with GH), IGF-1 plays a role in postnatal growth and development and may have several other actions:

- It helps in neuroprotection and regeneration in the adult CNS (by improving metabolism, dendritic growth, learning, and memory).
- It is involved in the regulation of longevity (Chapter 3).
- Studies in old mice (regardless of their diet) show a significant loss in the total number of cells in the supraoptic and paraventricular nuclei of the hypothalamus. However, when only the IGF-1 sensitive cells (i.e., cells that are binding to the IGF-1R) are considered, the IGF-1 cells are selectively protected in the older, calorie-restricted mice as compared to the older, fully fed mice (66,67).

Maintaining IGF signaling may provide the persistent paracrine growth factor activity necessary for delaying neuronal and neuroglial degeneration associated with aging. Alternatively, the maintenance of IGF-1 signaling in calorie-restricted mice may simply be an adaptive response to diminished energy availability. Caloric restriction may be energy conserving since it selectively promotes the loss of cells not critical to the survival of the whole organism, while, at the same time, preserving IGF cells, thereby reducing overall energy expenditure and perhaps prolonging the life span (Chapter 23).

■ Gonadotropins and Thyrotropin

Gonadotropins (Gn) undergo significant changes with aging in males and, particularly, in females. These changes are discussed in Chapters 10 and 11 in relationship to their role in aging of the respective target peripheral endocrine glands. Likewise, changes in thyrotropin-releasing hormone (THRH) (67) and thyroid-stimulating hormone (TSH) are discussed in Chapter 12.

■ Prolactin

PRL stimulates lactation and has anabolic, diabetogenic, and lipolytic actions (68). In humans (in males), plasma PRL levels increase with aging, perhaps because of the reduction in hypothalamic DA (the hypothalamic inhibitor of hypothalamic PRL release) with aging and the high incidence of pituitary PRL-secreting tumors. Low PRL levels in old women may be attributable to low estrogen levels after menopause (68). Further, dampening of day and night PRL levels, combined with declining rhythmicities of GH, adrenal, thyroid, pituitary, and pineal secretions, and the cessation of ovarian cyclicity, contribute to the progressive failure of chronobiologic regulations with aging (Chapter 13).

■ Vasopressin (ADH) and Oxytocin

ADH and oxytocin are small peptides secreted by magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus and transported within the axons to the posterior lobe of the pituitary, where the peptides are stored before being released into the circulation (Fig. 13). Within each hypothalamic nucleus, some neurons produce oxytocin and others ADH. The peptides are synthesized as part of larger precursor molecules (neurophysins) and are secreted in response to neuronal stimulation. In response to stress, ADH secretion stimulates the release of ACTH from the anterior pituitary, and both stimulate the adrenal cortex.

In aging rats (except perhaps in the very old), vasopressin- and oxytocin-secreting neurons are largely spared the morphologic changes that occur in neurons in most other hypothalamic nuclei (69,70). Some of the changes that occur have been related to functional decrements in the secretory activity of neurons in the hypothalamic, paraventricular, and supraoptic nuclei. Degenerating neurons often alternate with hypersecreting neurons, which compensate for cell loss and impaired function; this diverse aging pattern may account for the disparate observations of low, high, or unchanged hormone levels (69,70).

The principal action of vasopressin is to promote the retention of water by the renal distal tubules and collecting ducts (Chapter 18). The principal actions of oxytocin in stimulating contraction of smooth muscle of the uterus during delivery and the mammary gland during lactation are thought to be relevant primarily to the reproductive years. *However, oxytocin and vasopressin have significant CNS actions: they are reported to ameliorate long-term memory and attention impairments, neural connectivity, and social behaviors (71).* Intraventricular administration of oxytocin reduces levels of anxiety behavior and HPA responses to stress in female rats (72,73). If expressions of anxiety and stress do increase with aging for certain individuals, these individuals may benefit from oxytocin administration (69–73).

■ STRESS AND ADAPTATION

Successful survival of each organism depends on an environment favorable to the optimal expression of the organism's function. This expression is crucial for single-celled organisms and even more so for multicellular, complex organisms. For humans, the environment is comprised of both external conditions (e.g., atmospheric temperature, food availability, social interrelations) and internal conditions (e.g., metabolism, coordination of regulatory signaling among bodily systems, integration of multiple cellular and molecular functions). Thus, maintenance of a constantly stable internal environment in response to internal or external challenges (stress) is key to an individual's survival and reproduction (Table 3). Closely related to these concepts *is the idea of homeostasis, which refers to the body's "ideal steady state," or a "constant" internal environment (Box 4).* Since in order to survive and reproduce, an organism must vary the parameters of its internal environment to suit environmental demands, homeostasis can be achieved only through dynamic adjustments that reflect repeated fluctuations of various physiologic systems. *The term allostasis refers to these fluctuations and adjustments necessary for maintaining homeostasis* (Table 4) (79).

The cumulative effects of stress may affect health and longevity of the individual organism. The goal of "stability through change" or "homeostasis through allostasis" is attained by paying a long-term price in terms of decreased function and increased pathology. *Allostatic load captures the idea that over the life course, the body's response to stress carries a cumulative physiological toll that affects multiple biological systems.* Given the multitude and variety of environmental changes/challenges, allostasis must continuously be active in order to maintain homeostasis. *With aging, the allostatic efficiency may decline or deviate from what is optimal, thereby endangering homeostasis and generating abnormal (pathologic) responses and diseases.* Ultimately, then, the build-up of allostatic load might contribute to the increasing morbidity and mortality of old age (Tables 4 and 5).

Unlike allostatic load, which focuses on the negative consequences of some types of stress, *the concept of "hormesis" refers to the health-enhancing aspects of other types of stress. That is, a stress of low severity and/or short duration can promote survival and longevity by boosting the efficacy of physiologic adaptation and the reparation of health injuries, eventually inflicted by severe and long-lasting stress.* With the decoding of the human genome, physiologic genomics (i.e., gene expression that articulates the return to an optimal state after stress) is expected to provide the important integrative link between one or several genes and their function(s) in regulating the responses of the living organism to the environment in which the organism lives (Chapter 3). It is important to note that the idea that some amount of stress may be good for an organism has yet to be fully appreciated (or operationalized) in the allostatic-load literature.

The impact of the hormonal changes with aging on the ability of the individual to adapt and survive has generated a number of theories based on the hypothesis that specific endocrine signals, together with neural and immune signals (probably genetically linked), may direct aging and death. Neuroendocrine and, more recently, neuro-immuno-endocrine theories propose that aging is not due to intrinsic deteriorative processes in all cells or molecules, but rather to a programmed regulation by "pacemaker cells," perhaps situated in the brain (particularly, the hypothalamus) and acting through neural, immune, and endocrine signals (1,28,83–86). These signals might orchestrate the passage from one stage of the life span to the other, thereby timing the entire life cycle, including development, growth, maturation, and aging.

■ The Role of the HPA Axis in Response to Stress

A cornerstone of stress physiology is that widely different types of stress (e.g., physical, social, emotional) induce a series of responses that are mediated through adrenal (both adrenocortical and adrenomedullary) stimulation (83–86). Responses to stress involve the participation of some of the hormones of the adrenal cortex together with those of the adrenal medulla (as discussed in earlier sections). Most animal species so far studied, including humans, show increased glucocorticoid levels in response to stress and administered CRH or ACTH. *With removal of the adrenal gland in experimental animals or with a deficiency of the adrenal cortex in some diseases in humans (i.e., Addison's disease), defense mechanisms against stress fail to take place, and this failure leads to death.*

The glucocorticoid levels in old animals in response to stress may be lower or higher than in young animals, but, in many cases, differences with aging are small or absent. In humans, studies indicate that increased plasma cortisol in response to ACTH is preserved in old individuals. In contrast, the response of DHEA to ACTH appears to be significantly reduced with aging. Similarly, stimulation of aldosterone secretion leading to increased reabsorption of sodium from the urine and to sodium conservation in the body is less efficient in older subjects compared to younger ones (Chapter 18).

In vitro experiments show that corticosterone secretion from isolated adrenal cortical cells of old rats (24 months of age) is less responsive than that of young rats (three months of age) to a synthetic subunit of ACTH and to cyclic adenosine monophosphate (cAMP). Such experiments suggest that the intracellular changes with aging involve impaired steroidogenesis or receptor function, perhaps secondary to telomerase expression (87,88) or increased free radical production and membrane alterations.

Other tests indicate that the feedback mechanisms for ACTH control as well as the stimulatory action of ACTH on adrenocortical secretion are maintained in older men and women. Given the extreme heterogeneity of aging processes in adrenocortical as in many other functions, it appears that some old individuals remain quite capable of allostatic adaptation.

It is notable that in the case of exposure to stress, the activation of the HPA axis has precedence over all other neuroendocrine, hypothalamic, and pituitary functions that are not directly related to stress. Since survival represents the first objective of the stress-endangered individual, the hypothalamus and the pituitary respond by establishing a priority for

BOX 4 *Historical Notes: The "Milieu Interieur," Homeostasis, Allostasis, and Hormesis*

The French physiologist *Claude Bernard* (1813–1878) published, a book on the similarity of requirements for life in animals and plants (74). In this book, he formulated what was to be a landmark in the history of modern physiology, the concept of the "milieu interieur" (internal environment); *the preservation of the constancy of the internal environment is essential to the stability of the living organism, notwithstanding any external change.* He further stated that all vital body functions, varied as they are, act in concert to preserve constant the conditions of life in the internal organization.

Another physiologist, *Walter B. Cannon* (1871–1945), published *The Wisdom of the Body* (75), in which he analyzed the mechanisms of the internal regulation of body activity and coined the word "*homeostasis*" to indicate a relatively stable state (steady state) of equilibrium among the various functions of an organism in its response to changes in the environment. He underlined the importance of the autonomic nervous system, specifically, the sympathetic nervous system in the "fright, flight, or fight" reaction of an individual facing a threat.

In 1948, *Hans Selye* (1907–1982), published the first of several books on stress (76,77), in which he described the important role of the hypothalamo-pituitary-adrenal axis in mediating the responses of the organism to different types of stress in order to preserve the constancy and the stability of body functions. From the efficiency of these two sets of responses would depend the success or failure of the organism to adapt. In the absence of the adrenal gland (e.g., by surgical removal, or pathologic insufficiency), neither of these responses would occur, and the animal would not adapt and die.

Responses to stress could be grouped into three sequential phases as part of a general adaptation syndrome characterized by (*i*) an initial phase in which defense mechanisms are acutely challenged (alarm reaction), (*ii*) a period of enhanced adaptive capacity (stage of resistance) and, (*iii*) the loss of the capacity to adapt (stage of exhaustion). Repeated exposures to stress may either lead to successful adaptation with more efficient ability to withstand subsequent stress or induce pathology, the so-called "diseases of adaptation" (e.g., cardiovascular diseases, immunosenescence) and shorten life.

Among the contemporary investigators, *Roger Guillemin*, a former student of Hans Selye, was the first to identify the hypothalamic source and function of the hypophysiotropic hormones for which he received the Nobel Prize in 1977 with Andrew V. Schally, who described the chemical structure of these hormones, and with Rosalyn S. Yalow, who developed the radioimmunoassay technique for their identification. In 1992, *Robert M. Sapolsky* extended the neuroregulation of stress to include the brain limbic centers (e.g., hippocampus, amygdala) involved in behavior, emotions, and memory (13,78). Glucocorticoids administered in high doses would be toxic, particularly to hippocampal neurons rich in glucocorticoid receptors and cause their death. Hippocampal cells, under no-stress conditions, inhibit corticotropin-releasing hormone (CRH) release from the hypothalamus; therefore, loss of hippocampal neurons would result in increased CRH secretion and consequently of adrenocorticotropic hormone (ACTH) (from the anterior pituitary) and of glucocorticoids (from the adrenal cortex). His "glucocorticoid cascade hypothesis of aging" implicated that the resulting high glucocorticoid levels would be responsible for or contribute to some of the increased pathology of aging.

In 2002, *Bruce S. McEwen*, a neuroendocrinologist, in collaboration with the epidemiologist *Teresa E. Seeman* demonstrated that the cumulative effects of stress may affect negatively the health and longevity of individual organisms (79,80). They stated that the goal of "stability through change" is attained by paying a price: decreased function and increased pathology, the so-called "allostatic load."

Alongside the classical concept of homeostasis and the more recent one of allostasis other studies focus on a more favorable outcome. Thus in 1991, the radiobiologist *Thomas L. Luckey*, comparing the effects of small doses of radiation to those of large doses on animal longevity, demonstrated that small doses prolonged longevity while large doses shortened it. Accordingly, he suggested to add the name of "hormesis" be added to the vocabulary of the effects induced by stress (81). This theme was further developed by several investigators among whom the cell biologist *Gordon J. Lithgow* demonstrated in 2001 that manipulation of insulin/insulin-like growth factor-1 receptor in worms could significantly increase resistance to stress and prolong life (82). The role of hormesis in extending longevity and in increasing resistance to stress seems to be applicable to other animal species (Chapter 3) and continues to be actively studied by many other investigators to maximize the positive effects of stress.

1. an increased secretion of CRH which, in turn,
2. insures a higher secretion of ACTH from the pituitary, and
3. a higher secretion of glucocorticoids from the adrenals.

Simultaneously, sympathetic stimulation, initiated in the hypothalamus, directs the adrenomedullary cells to release more catecholamines. These priorities for stimulation of the HPA axis result concomitantly with an inhibition of the secretion of gonadotropin-releasing hormone, GnRH, and of sexual function in males and females. As shown in Table 6 and Figure 14, under conditions of stress, GHRH secretion is inhibited and body growth impaired.

TABLE 4 Stress, Homeostasis, Allostasis, and Allostatic Load

Stress: threats to physiologic equilibrium (i.e., homeostasis) in the form of internal or external challenges
Homeostasis: an "ideal steady-state" in which a constant internal environment is maintained in order to permit optimal functioning
Allostasis: the process by which an organism actively varies the parameters of its internal milieu to match them appropriately to environmental demands
Allostatic load: the long-term physiological cost to the body stemming from attempts at adaptation (i.e., allostasis). Allostatic load supposedly builds up in a cumulative fashion throughout the life course and affects multiple body systems (e.g., the metabolic, the immune, and the cardiovascular systems)

■ Physiologic Responses to Stress

On the one hand, exposure to a stress elicits physiologic responses that are directed specifically to that stress. On the other, these responses are simultaneously accompanied by a group of responses (e.g., the fright, fight, or flight responses, Table 2) that are always the same, irrespective of the type of stress (Table 3), and depend on stimulation or inhibition by hormonal signals. A consequence of HPA stimulation and increased levels of CRH, ACTH, vasopressin, and cortisol is a concomitant decrease in the secretion of the other hormones originating from the anterior pituitary, particularly a reduction in GH and Gn. Thus, while the stress response produces short-term benefits, it also results in a delay in growth and an inhibition of sexual and reproductive function (Fig. 14). While many of these allostatic responses may be regulated by the HPA axis (79,80), other physiologic systems are involved as well and they may be responsible for some of the consequences of stress (Tables 6–8). Thus, homeostatic competence, as expressed through the HPA axis in response to stress, provides a "panoramic view" of overall physiologic performance (83–88).

As discussed earlier in this chapter, under resting (basal) conditions, few changes occur in HPA function in old age. The nervous, neuroendocrine, and immune systems have many interrelated responses and work together to preserve homeostasis (89–95). However, under stress, evidence of decreased physiologic, competence is plentiful. The increased risk of death following stress in the elderly is well acknowledged and needs no documentation here. Older individuals are less resistant than younger ones to excessively cold or warm temperatures because of the progressive deterioration of thermoregulatory mechanisms that occurs with aging (Chapter 12). Equally diminished is the capacity of older persons to adapt to infections, hypoxia, traumatic injury, excessive exercise, and physical work, all representing types of stress that require complex physiologic adjustments. Emotional stress in the old is also capable of triggering or aggravating a series of physical ailments that, superimposed on an already debilitated state, may contribute to disease and death (Fig. 15).

TABLE 5 Pathophysiologic Responses During and After Stress

During stress
Energy storage ceases because of
↑ Sympathetic activity
(i.e., increased vigilance/arousal)
↓ Parasympathetic activity
↓ Insulin secretion
Use of stored energy is facilitated because of
↑ Glucocorticoid secretion
↑ Epinephrine/norepinephrine secretion
↑ Glucagon secretion
After stress
If adaptation is inadequate, poor health may result (e.g., the body cannot completely restore the loss of stored energy used during the stress response)
Examples of consequences of inadequate adaptation
Muscle wasting
Diabetes (type 2)
Ulcers, colitis, diarrhea
Inhibition of growth (in childhood)
Osteoporosis (in old age)
↓ GnRH, ↓ testosterone

Abbreviation: GnRH, gonadotropin-releasing hormone.

TABLE 6 Functions Stimulated or Inhibited by Physical/Psychological Stress

Functions stimulated by stress	Functions inhibited by stress
All functions immediately necessary for defense and survival are increased	All functions not immediately necessary for defense and survival are decreased
Cardiovascular	Whole-body growth
↑ Cardiac rate	Appetite (anorexia)
↑ Blood pressure	Reproductive function and sex drive
↑ Blood coagulation	Circulation in tissues not involved in stress response
↑ Redistribution of blood from peripheral (skin) and internal systems (gastrointestinal) to heart, skeletal muscles, brain	Response to pain
Respiratory	Immune function
↑ Respiratory ventilation	↓ Thymus size
Metabolic	↓ Thymic hormones and cytokines
↑ Glycogen mobilization	
↑ Glycemia	
↑ Lipolysis	
Hormonal	
↑ CRH, ACTH, and glucocorticoids	
↑ Vasopressin and NGF[a]	
↑ Catecholamines (E and NE)	

[a]Taken as an example of a growth-promoting, paracrine factor (Chapter 6).
Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; E, epinephrine; NE, norepinephrine; NGF, nerve growth factor.

■ Allostasis or Hormesis? Janus the Two-Faced God

As mentioned in an earlier chapter (Chapter 3), an important indicator of health is the number of illnesses that simultaneously affect the same individual. To capture this dimension of health, comorbidity indices are being utilized to assist in evaluating the so-called "morbidity load" (96). The parameters of one such index are presented in Table 7. A deviation in these parameters from normal values, which may result from repeated exposures to stress, may constitute greater *allostatic load* and put an individual at greater risk for a number of health problems, including cognitive and physical declines (Table 8) (79).

Regarding whether the current measures of allostatic load accurately capture stress experienced over the life course, the evidence is mixed (Box 4). For example, one study investigating this question analyzed a nationally representative data set from

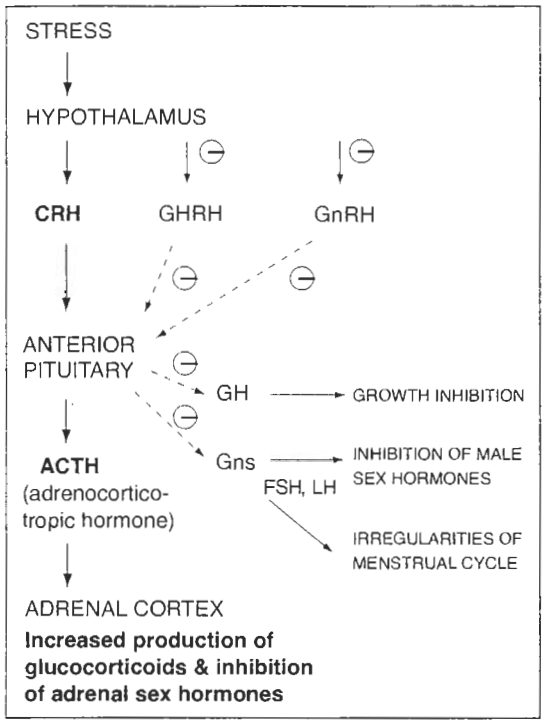

FIGURE 14 During stress, the priorities of the secretions of the hypothalamo-pituitary-peripheral endocrine axes are shifted in favor of the HPA axis. During stress, whereas the HPA axis is stimulated, the secretion of the other hormones is drastically reduced. This shift may explain the decrease in growth and insufficiency of gonadal function during stress. *Abbreviations*: HPA, hypothalamo-pituitary-adrenocortical; FSH, follicle-stimulating hormone; LH, luteinizing hormone (women); GH, growth hormone; CRH, corticotropin-releasing hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; Gns, gonadotropins.

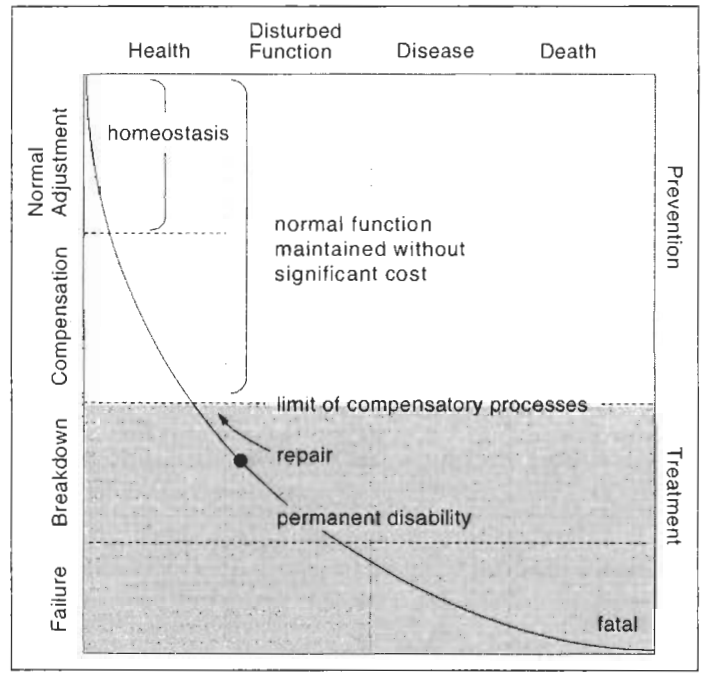

FIGURE 15 Progressive stages of homeostasis from adjustment (health) to failure (death). In the healthy adult, homeostatic processes ensure adequate adjustments in response to stress, and, even for a period beyond this stage, compensatory processes are capable of maintaining overall function without serious disability. When stress is exerted beyond the compensatory capacities of the organism, disability ensues in rapidly increasing increments to severe illness, permanent disability, and death. When this model is viewed in terms of homeostatic responses to stress imposed on the aged, and to aging itself, a period when the body can be regarded as being at the point of "limit of compensatory processes," it is evident that even minor stresses are not tolerable and the individual moves rapidly into stages of breakdown and failure.

Taiwan that included individuals between the ages of 54 to 91. Contrary to expectation, a number of indicators of a stressful life history (e.g., low education, widowhood, living alone, subjective reports of familial stress) were not linked to an allostatic load measure that focused on the neuroendocrine biomarkers (21). *One interpretation of these results is that given a life history of challenge, at older age, the body still retains its ability to maintain homeostasis and respond to new types of stress (97).*

According to the concept of *hormesis*, small (moderate) doses of stress have stimulatory actions that provide benefits for the organism (Box 4) (81). As mentioned in Chapter 3, manipulation of metabolic or hormonal signaling in various animal species increases longevity as well as resistance to stress. Thus, stress may have two different types of influences, positive and negative. This dual action is reminiscent of Janus, the Roman god whose statue was placed outside the gate of large and small Roman cities. One face, smiling and benevolent, looked toward the town, presumably wishing prosperity and health. The other face, frowning and malevolent, looked toward the surrounding countryside, presumably intimidating any would-be attackers. In other words, in humans, a moderate stress of short duration may be protective, whereas a severe stress of long duration may be harmful (Fig. 16).

TABLE 7 Some Parameters Used to Operationalize Allostatic Load

1, 2. Systolic and diastolic blood pressure (indices of cardiovascular activity)
3. Waist-hip ratio (index of long-term metabolic/lipid deposition)
4, 5. Serum HDL and total cholesterol levels (indices of atherosclerotic risk)
6. Blood plasma levels of total glycosylated hemoglobin (index of glucose metabolism)
7. Serum DHEA sulfate levels (index of HPA inhibitor/antagonist)
8. 12-hr urinary cortisol excretion (index of 12 hr integrated HPA activity)
9, 10. 12-hr urinary norepinephrine and epinephrine excretion levels (index of 12-hr integrated sympathetic activity)

Abbreviations: DHEA, dehydroepiandrosterone; HDL, high-density lipoprotein; HPA, hypothalamo-pituitary-adrenal.
Source: Adapted from Ref. 79.

TABLE 8 An Operationalization of Allostatic Load

Elevated physiologic indices (indicating individuals at risk)
Systolic blood pressure: ≥ 140 mmHg
Diastolic blood pressure: ≥ 80 mmHg
Waist-hip ratio: ≥ 0.94
Total cholesterol/HDL ratio: ≥ 5.0
Total glycosylated hemoglobin level: ≥ 6.5%
Urinary cortisol level: ≥ 25.7 mg/g creatinine
Urinary epinephrine level: ≥ 5 mg/g creatinine
Urinary norepinephrine level: ≥ 48 mg/g creatinine
Lowered physiologic indices (indicating individuals at risk)
HDL cholesterol level: ≤ 1.45 mmol/L
DHEA level: ≤ 2.5 μmol/L

Abbreviations: DHEA, dehydroepiandrosterone; HDL, high-density lipoprotein.
Source: From Ref. 79.

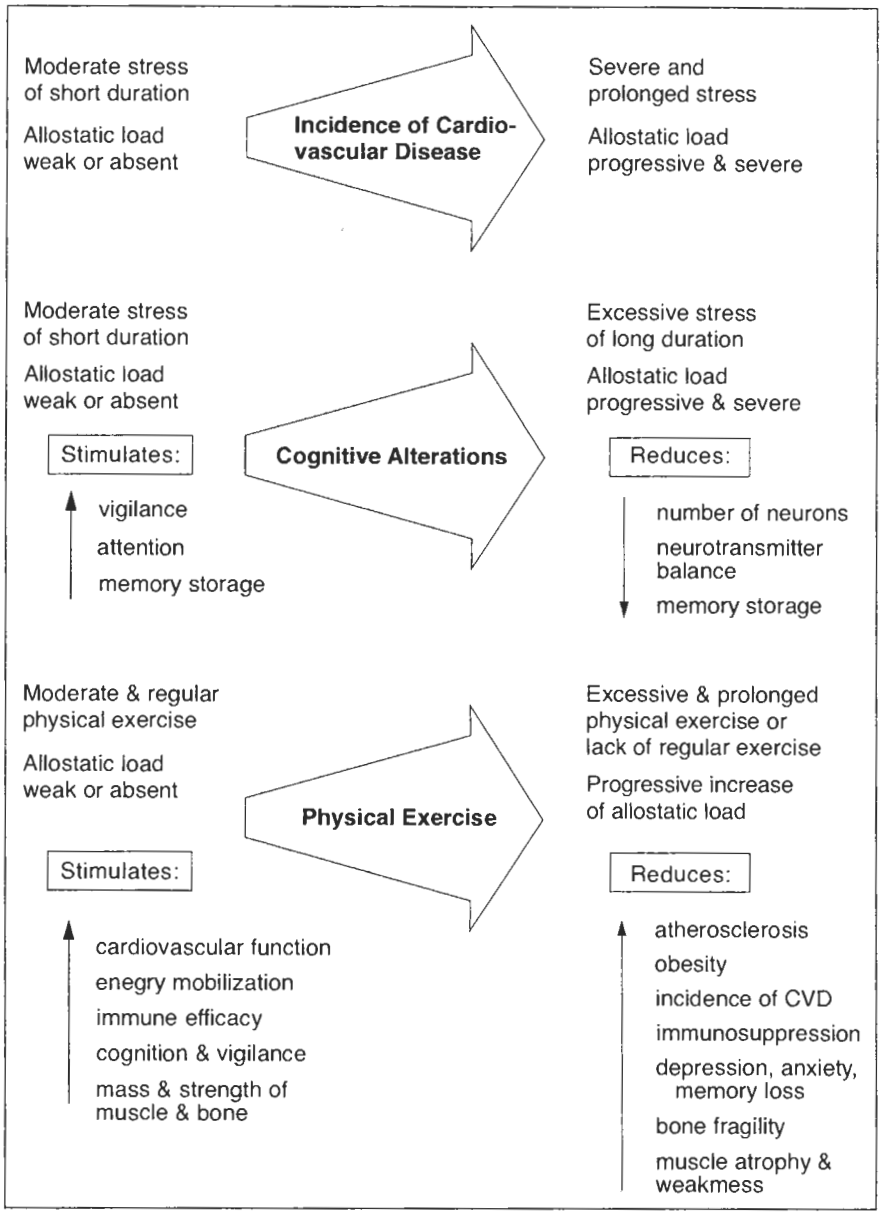

FIGURE 16 Dual action of stress on the incidence of CVD, cognitive alterations, and physical exercise. With moderate stress of short duration, the allostatic load is weak, absent, or may induce beneficial "hormetic" effects (the *left side* of the figure). When stress is severe and prolonged, the allostatic load is progressive and severe, and induces untoward effects, leading to an increase in pathology (the *right side* of the figure). *Abbreviation*: CVD, cardiovascular disease.

Some of the beneficial effects of stress are listed in Table 9. These effects are mediated through several mechanisms such as the (*i*) reduction of free radical production and accumulation (Chapter 5) and the (*ii*) increased production of HSPs. These HSPs act as chaperones by assisting other proteins in the cells to fold in a way that helps in the maintenance of the cells. In addition, HSPs play an important role in immune reactions by modulating antigens and the activation of lymphocytes, cytokines, and natural killer cells (98–104).

■ Strategies for Coping with Stress

Although a number of stress-reducing interventions are often outside of an individual's control (105), *stress management* can still lead to salutary states of adaptation by several approaches: *physical* (e.g., optimal physical exercise, responsible diet, Chapter 24), *pharmacological* (e.g., administration of neurotransmitter agonists, neurotransmitter antagonists, calcium blockers), and *psychological* (e.g., improvement of social networks, finding outlets for frustration, manipulation of feelings). Given the wide heterogeneity among individuals, a wise approach to stress management is a customized set of

TABLE 9 Beneficial Effects of Hormesis[a]

↑ DNA repair
↑ Chaperones
↑ Immune-system competence
↑ Neurologic acuity
↑ Neuromuscular activity
↑ Better memory
↑ Resistance/adaptation to stress
↓ Oxidative stress

[a] Hormesis follows exposure to mild levels and short durations of stress.

hygienic habits that takes into account specific knowledge of both the specific genome and the environment.

In closing, beyond specific techniques for stress management, it is important to remember that the plasticity of our functional responses persists well into old age, and this should give us optimism in our abilities to cope with challenges. It is also important to remember that adapting to our environment is a fundamental and inescapable activity, so, as Selye would say, we ought to try to "learn to enjoy our stress."

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