PRINCIPLES AND PRACTICE OF ENDOCRINOLOGY AND METABOLISM

THIRD EDITION

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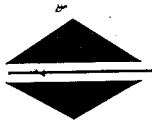

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CHAPTER 73

CORTICOSTEROID ACTION

PERRIN C. WHITE

GENERAL MECHANISMS OF ACTION

The steroid hormones, vitamin D, retinoic acid, and the thyroid hormones all share a similar mechanism of action.[1,2] These hormones diffuse through the target cell membrane and interact with a specific receptor protein for each hormone. The activated hormone-receptor complex binds to specific DNA sequences, the hormone-responsive elements (HREs), which are usually located in the 5' flanking region of each hormone-responsive gene. These complexes may also bind to other transcription factors. The binding of the hormone-receptor complex to these DNA sequences or transcription factors leads to selective increases or decreases in gene transcription. The altered protein levels that result from this change in transcription rate are responsible for the hormonal response seen in that particular tissue.[3]

At least six classes of *steroid receptors* exist, corresponding to the known bioactivities of the steroid hormones: glucocorticoid, mineralocorticoid, progestin, estrogen, androgen, and vitamin D. Additional "orphan" receptors of incompletely understood function are found that bind related compounds such as androstanes.[4] Steroid receptors belong to a larger superfamily of nuclear transcriptional factors that includes the thyroid hormone and retinoic acid receptors. All of these receptors share a common structure that includes *a carboxy-terminal ligand-binding domain and a midregion DNA-binding domain*. The latter domain contains two "zinc fingers," each of which consists of a loop of amino acids stabilized by four cysteine residues chelating a zinc ion.[5]

Unliganded steroid hormone receptors shuttle between the cytoplasm and the cell nucleus. Importation into the nucleus is an energy-dependent process. This process requires one or more nuclear localization signal sequences on the receptor, which consist of clusters of basic amino-acid residues located in or near the DNA-binding domain. When not occupied by ligand, the various hormone receptors differ in their propensity to be transported to the nucleus. For example, the estrogen receptor is predominantly located within the nucleus, whereas the unoccupied glucocorticoid and mineralocorticoid receptors are found mainly in the cytosol.[6]

The cytosolic glucocorticoid receptor, when not bound to its heat shock protein (HSP) 90 and one molecule each of HSP 70 and HSP 56 (immunophilin).[7] Binding of ligand changes the conformation of the receptor and, thus, has several effects. HSP 90 is associated with the unliganded glucocorticoid receptor at the ligand-binding domain and dissociates from the receptor complex after glucocorticoid binds to the receptor. A dimerization region that overlaps the steroid-binding domain is exposed, promoting dimerization of the occupied receptor. Finally, a hormone-dependent nuclear localization signal located in a "hinge" between the DNA and steroid-binding domains is activated, which leads to increased importation of occupied receptors into the nucleus. The occupied receptors are then able to bind DNA and/or other transcription factors and modulate transcription of various genes.[8,9]

Glucocorticoids affect transcription of a wide variety of genes through several different mechanisms.[8] First, the glucocorticoid-receptor complex can stimulate transcription by binding to specific glucocorticoid-responsive elements (GREs) in the 5' flanking region of glucocorticoid-responsive genes. GREs, like other specific hormone response elements, are often imperfect palindromes (in a palindrome, the two complementary strands of a DNA molecule, when "read" in opposite directions, have the identical sequence). Most often, GREs are variants of the sequence GGTACAnnnTGTTCT, where "n" is any nucleotide. The existence of two "half-sites" separated by three nucleotides suggests that glucocorticoid receptors interact with GREs as dimers, with one monomer binding to each half-site. However, many GREs consist of isolated half-sites or half-sites with variable spacing between them. Moreover, marked variations in sequence can be tolerated in one half-site. Thus, monomeric glucocorticoid receptors can also bind DNA, but the binding can apparently be stabilized by interactions with other bound receptor molecules or other transcription factors. Thus, binding of the monomeric receptor to one half-site markedly increases the ability of a second monomer to bind to the other half-site.

The interaction of the glucocorticoid receptor and DNA has been studied in detail by x-ray crystallography and nuclear magnetic resonance techniques.[5] The two zinc fingers form a single domain. Alpha helices adjacent to each finger on the carboxy-terminal side are oriented perpendicularly to each other; the first helix fits into the major groove of the DNA helix and makes direct contact with bases. The tips of both fingers contact the phosphate backbone, and the second finger also mediates DNA-dependent dimerization of the receptor.

GREs cannot constitute the only DNA sequences mediating the transcriptional effects of glucocorticoids. GREs are indistinguishable in sequence from the elements binding mineralocorticoid, progestin, and androgen receptors, and these receptors are >90% identical in amino-acid sequence in their DNA-binding domains. However, the amino-terminal domains of these receptors are <15% identical in amino-acid sequence, and at least some interactions with other transcriptional factors are mediated by this domain.[10]

As a second type of effect, glucocorticoid receptors can inhibit or activate transcription by interacting with other transcription factors.[8,9,11] In particular, they can regulate gene activity by repressing gene transcription mediated by "AP-1" or NF-κB elements in the regulatory regions of some genes. These AP-1 and NF-κB sites bind cFos-cJun or RelA-p50 heterodimers, respectively. The ligand-bound glucocorticoid receptor monomer and/or dimer interacts with AP-1 or NF-κB and prevents them from exerting their transactivational effects on the genes they normally regulate. AP-1 and NF-κB serve as intracellular messenger systems for many growth factors and inflammatory cytokines, respectively. The profound antigrowth and antiinflammatory effects of glucocorticoids are exerted to a great extent via transrepression of these transcription factors. In addition, glucocorticoid receptors may modulate effects of the

Unlike glucocorticoids, mineralocorticoids do not appear to interfere with cFos-cJun or NF-κB binding. This functional difference may be localized to the amino-terminal domain of the receptor.[10]

Two new classes of nuclear proteins that influence the transactivational activity of nuclear receptors have been identified and collectively called *coregulators*.[12,13] According to their ability to potentiate or diminish the activity of nuclear receptors, they are respectively called *coactivators* and *corepressors*. Known coregulators are large proteins with many functional domains. One could think of coactivators as bridges between the DNA-bound nuclear receptor and components of the transcription machinery, such as ancillary factors of DNA polymerase II, that stabilize and hence stimulate the activity of the initiation complex. In addition, coactivators have enzymatic activities that promote transcription, such as histone acetyl-transferase activity, which loosens the DNA double helix from the nucleosome and allows the polymerase complex to exert its activity.[14] On the other hand, corepressors prevent the nuclear receptor from binding to DNA and/or transactivating their target genes and have enzymatic activities that impede transcription, such as histone deacetylase, which strengthens the interactions of the DNA with the nucleosome. Coregulators are expressed in a tissue-specific fashion and have varying degrees of specificity for particular nuclear receptors. Some of these proteins serve as coregulators of other transcription factors, such as AP-1, NF-κB, and the Stats, and hence serve as cross-points between different signal transduction systems in the cell.

Several factors regulate tissue-specific effects of steroids at several levels both before and after the receptor. Most obviously, hormone receptors are widely but not ubiquitously expressed, and a particular class of steroid fails to have effects on cells that do not express the corresponding receptor. Of physiologic importance, enzymes may increase or decrease the affinity of steroids for their receptors and thus modulate their activity. For example, the mineralocorticoid receptor has identical affinities in vitro for cortisol and aldosterone, yet cortisol is a weak mineralocorticoid in vivo. This discrepancy may result from the action of 11β-hydroxysteroid dehydrogenase, which converts cortisol to cortisone. Cortisone is not a ligand for the receptor, whereas aldosterone is not a substrate for the enzyme. Pharmacologic or genetic inhibition of this enzyme allows cortisol to occupy renal mineralocorticoid receptors and produce sodium retention and hypertension.[15]

Whereas different steroids may share bioactivities because of their ability to bind to the same receptor, a given steroid may exert diverse biologic effects in different tissues. The diversity of hormonal responses is determined by the different genes that are regulated by the hormone in different tissues. Glucocorticoids, for example, have primarily GRE-mediated metabolic effects in liver and mainly anti–NF-κB–mediated antiinflammatory properties in lymphoid tissue.[16]

In addition to the actions resulting from the binding of steroids to nuclear steroid receptors, some effects might be mediated through other mechanisms. Such effects often take place with extreme rapidity (milliseconds to minutes) and/or have been documented not to require protein synthesis, a sine qua non of the transcriptional effects mediated by nuclear-hormone receptors. These effects have been most extensively documented for 1,25-dihydroxyvitamin D_3, progesterone, and aldosterone; they appear to involve second messengers systems including protein kinase C, intracellular calcium levels, nitric oxide, and tyrosine kinases.[17] Thus far, however, no steroid-specific membrane receptors have been isolated or cloned. (Also see Chaps. 4 and 54.)

ACTIONS OF THE GLUCOCORTICOIDS

Glucocorticoids are essential for survival. The term *glucocorticoid* refers to the glucose-regulating properties of these hormones, but they include an important role in carbohydrate, lipid, and protein metabolism (Table 73-1). They also regulate immune, circulatory, and renal function. They influence growth, development, bone metabolism, and central nervous system (CNS) activity.

In stress situations, glucocorticoid secretion can increase up to almost 10-fold.[18,19] This increase is believed to enhance survival by increasing cardiac contractility, cardiac output, sensitivity to the pressor effects of the catecholamines and other pressor hormones, work capacity of the skeletal muscles, and capacity to mobilize energy through gluconeogenesis, proteoly-

TABLE 73-1.
Major Glucocorticoid Actions

METABOLIC EFFECTS
Carbohydrate
Increase blood sugar
Increase gluconeogenesis in liver and kidney
Increase hepatic glycogenesis
Increase cellular resistance to insulin; decrease glucose uptake in tissues
Lipid
Increase lipolysis
Protein
Increase proteolysis
IMMUNOLOGIC EFFECTS (PHARMACOLOGIC LEVELS)
Stabilize lysosomal membranes
Block bradykinin, histamine, interleukin-1 and interleukin-2, plasminogen-activating factor
Decrease vascular permeability
Increase polymorphonuclear (PMN) cell release from bone marrow:neutrophilia
Block PMN diapedesis, chemotaxis, and phagocytosis
Deplete circulating lymphocytes:lymphocytopenia affecting T cells more than B cells
Decrease antibody formation from B lymphocytes
Deplete circulating monocytes:monocytopenia
Deplete circulating eosinophils:eosinopenia
Decrease thymic and lymphoid tissue mass
Impair delayed hypersensitivity reaction
Decrease resistance to bacterial, fungal, viral, and parasitic infections
CONNECTIVE TISSUE EFFECTS
Decrease collagen formation
Impair granulation tissue formation and wound healing
CALCIUM AND BONE EFFECTS
Decrease serum calcium
Accelerate osteoporosis
CIRCULATORY EFFECTS
Increase cardiac output
Increase response to catecholamines
RENAL EFFECTS
Increase renal blood flow and glomerular filtration rate
Increase free water clearance
Inhibit vasopressin
CENTRAL NERVOUS SYSTEM EFFECTS
Increase mood lability
Cause euphoria
Produce psychosis
Decrease libido
Blunt thyrotropin and gonadotropin activity
EYE EFFECTS
May induce posterior subcapsular cataracts
GROWTH AND DEVELOPMENTAL EFFECTS
Inhibit skeletal growth (pharmacologic doses)
Mature surfactant, hepatic, and gastrointestinal systems

PMN, polymorphonucleocytes; *TSH*, thyrotropin.

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