

Receptors: Structure and Function

Dennis K. Stone, MD

Key to the coordination of the functions of individual cells within the intact organism is intercellular communication, a means by which the individual cell is regulated in its specialized functions in a manner that serves the integrated needs of the organism as a whole. This process of intercellular signaling is achieved through myriad molecules that interact specifically with their respective docking sites, or receptor proteins. In endocrine functions, circulatory hormones bind to high-affinity receptors in their target tissues, and induce a cascade of events that culminate in their defining effects on cell structure, function and growth. In paracrine functions, effector molecules exert more local effects by binding to nearby receptors to produce coordination and synchronization of function within a cluster of cells. Subsequent to binding of ligand, the receptor serves a transducing function, and signals to intracellular portions of itself, or other associated proteins, that ligand has been bound. This, in turn, activates specific effector pathways resulting in metabolic and structural changes in the cell that constitute the signature effect of the agonist (1).

Knowledge of the breadth and function of cellular receptors is burgeoning; as an example, several hundred G protein coupled receptors have been found in mammalian cells. In contrast, our understanding of receptor structure is generally indirect, and largely two dimensional. To date, no structure of any integral membrane receptor has been solved in entirety by crystallographic analysis, although soluble domains of some receptors have been crystallized, yielding insight into at least partial reactions carried out by these proteins. Despite this, investigations of the specifics of receptor structure and function have led to the definition of intracellular signaling pathways of universal importance. From the standpoint of pharmacotherapeutics, receptor molecules have become the most important of all potential drug target sites. In addition, the roles of defective receptor function in the pathogenesis of genetic and acquired diseases have

become increasingly apparent. Subsequent articles in this series describe in detail the molecular basis of receptor-based diseases. As an introduction, this review is focused on the most proximal aspect of these signaling pathways—the receptors themselves.

Receptors were first conceptualized by Ehrlich to explain the interactions of antigen and antibodies, and the binding of drugs in their target tissues. This lock-and-key model, prescient in its implications of tight binding affinities and specificity of receptor-ligand interactions, did not encompass a view of how receptor molecules could initiate changes in cellular functions. In 1984, a summary definition (2) of receptors set forth several key elements that further distinguished these proteins: “Receptors are proteins typically composed of several domains. They contain, by definition, at least one binding site for a natural ligand. Receptors interact with one or several of a variety of effector systems for which they must also possess recognition sites. A single effector system may connect with various receptors. The information for activating the effector system is entirely contained in the membrane receptor; the ligand, or specific anti-receptor antibodies, only act as triggers of receptor-mediated effects, often initiated by receptor change in conformation, micro-aggregation, redistribution, internalization or chemical modification.”

This characterization is itself incomplete, and does not encompass receptors responsible for the delivery and uptake of cellular substrates. In addition, it is now clear that many receptors have intrinsic enzymatic activities that are truly part of the “effector system” itself.

For the purpose of this review, receptors are divided into two basic classes. First are the “cargo” type receptors that serve to deliver key metabolic substrates, nutrients, and minerals to cells (3). Examples of these include the low-density lipoprotein (LDL) receptor, which serves as a docking site for circulating LDL particles, and the transferrin receptor, which binds iron-laden transferrin and ultimately facilitates iron transport into cells. A second broad class of receptors play an essential role in cellular signaling, and can be subclassified on the basis of the mechanism by which they activate signaling pathways within their receptor target cells.

One subclass of receptors engaged in signaling is distinguished by the presence of a cytosolic domain with intrinsic enzymatic activity. These types of receptors include receptors with intrinsic tyrosine kinase (insulin receptor) or tyrosine kinase associated activities (prolactin

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From the Division of Molecular Transport, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas.

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receptor) (4,5). Other receptors within this category have intrinsic guanylylase activity (atrial natriuretic peptide receptor), tyrosine phosphatase activity (CD45 protein), or serine/threonine kinase activity (TGF- β receptor) (6,7). A second subclass of receptors engaged in signal transduction have in common their association with heterotrimeric G proteins, which became activated by ligand binding to the receptor (8). A third subclass of these types of receptors initiates cellular signaling by their intrinsic channel activities, which allow, upon activation by ligand binding, the rapid movement of ions across cell membranes. The acetylcholine receptor of the synapse, which has intrinsic sodium channel activity, and the ryanodine receptor of sarcoplasmic reticulum are examples of this type of signal effector molecules (9,10). Lastly, the steroid hormone receptor superfamily, which includes receptors for vitamin D, steroid hormones, thyroid hormones, and retinoic acid, constitutes a subclass of receptors engaged in cell signaling. Receptors of this group are localized to the cytosol and nucleus, rather than the plasma membrane, and have specific ligand binding sites, as well as a DNA binding domain. When activated, these receptors serve as transcription regulatory factors (11,12).

The general structural and functional features of these classes of receptor are reviewed below.

CARGO-TYPE RECEPTORS

Cargo type receptors, such as the LDL receptor, reside on the plasma membranes of cells and serve as a mechanism whereby the cell can take up essential nutrients, in this case, cholesterol. Investigation of the clinical disorder familial hypercholesterolemia led to the identification of numerous mutations within the LDL receptor gene that cause this disease, as well as discovery of the basic process of receptor-mediated endocytosis itself (3,13).

After circulating LDL particles bind to the LDL receptor, the receptor-ligand complexes migrate laterally in the plasma membrane to cluster within clathrin-coated pits. Subsequently, these coated pits invaginate, and give rise to discrete clathrin-coated vesicles that contain within their interior the LDL particle bound to what was formerly the extracellular portion of the LDL receptor. Within about 90 seconds after internalization, clathrin is shed from these vesicles, and the now uncoated vesicles migrate and fuse with the endosomal compartment. Endosomes are acidic relative to the cytosol and have an internal pH of about 5.2. This acidity is critical to the processing of the endocytosed receptor-ligand complex, and in the case of the LDL receptor, and its cargo substrate LDL, acidification of the vacuole causes release of the LDL particle from the LDL receptor. Once this occurs, cholesterol is transferred from the endosomal compartment to lysosomes. Lysosomes are more acidic than en-

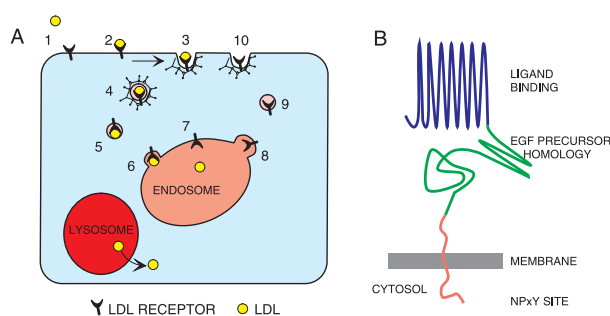


Figure 1. Receptor-mediated endocytosis as exemplified by the low-density lipoprotein (LDL) receptor. **Panel A:** Sequential steps in the uptake and processing of the LDL receptor are as follows: (1) The LDL receptor is resident on the plasma membrane. Circulating LDL binds to its receptor (2), and the receptor-ligand complex migrates to a clathrin-coated pit (3). The LDL-receptor complex is internalized in a clathrin-coated vesicle (4) that sheds its clathrin (5). The vesicle fuses with an endosome (6), and the acidity of the interior causes the LDL to dissociate from the LDL receptor (7). The LDL receptor begins to return to the plasma membrane (8,9), where it is reinserted into the plasma membrane (10). In addition, cholesterol is transferred from the endosome to the lysosome, where it is exported for cellular metabolism. **Panel B:** Model of the LDL receptor.

dosomes, with a steady-state pH of about 4.5. This acidity, in concert with a newly discovered carrier protein within the lysosomal membrane, facilitates the transfer of cholesterol from this compartment, making it available for cellular metabolism.

As part of the process of receptor-mediated endocytosis, the LDL receptor is reutilized; vesicles containing the emptied receptor bud from the endosome, and recycle to the plasma membrane. After fusion, the LDL receptor assumes its original topography, with the LDL binding site once again being exposed to the extracellular environment (3). Shown in Figure 1 is a representation of this process, as well as a structural model of the LDL receptor. As shown, the extracellular portion consists of a series of cysteine-rich repeats that form the actual LDL binding site. Other features of the protein include an EGF precursor homology domain that is essential for dissociation of LDL in the acidic endosome, a single transmembranous spanning region, and a small domain (NPxY) in the cytoplasmic tail that functions as an "internalization motif" (13). It has been shown that this particular sector is critical for the lateral migration of the LDL receptor in the plasma membrane to clathrin-coated pits and, ultimately for internalization of the receptor-ligand complex. Regulation of the LDL receptor occurs mainly at the level of transcription; reduction of cellular cholesterol, sensed within the endoplasmic reticulum, leads to an increase in mRNA encoding the receptor, and ultimately in the syn-

thesis of LDL receptors that serve to enhance the LDL-binding capacity of the cell.

Although many of the plasma membrane receptors that will be discussed below utilize this constitutive, receptor-mediated endocytotic pathway as part of their processing cycles, they differ fundamentally from the cargo type receptors in that they function not in the bulk transport of metabolic substrates, but rather in cell signaling. That is, these types of receptors serve to generate specific hormone or agonist-triggered responses. General features of these types of receptors include an extracellular ligand binding site that, when occupied, causes a conformational change in the cytosolic portion of the receptor molecule. This conformational change subsequently activates a variety of intracellular signaling pathways that is ultimately manifested in the ligand-specific effect on the cell. Although they differ in substrate specificity, structure, and distal effector pathways, they hold in common a high-affinity ligand binding site, and the essential functions of transducing, and amplifying, the signal arising from ligand binding. Each utilizes discrete signaling pathways to achieve their specific effects. In addition, these receptors have highly regulated mechanisms for deactivating that function to terminate the signaling process.

ENZYME LINKED RECEPTORS

Receptors with Intrinsic Kinase Activity

The members of this class of membrane receptors are distinguished as a subclass by the presence of an intrinsic tyrosine kinase activity within the receptor molecule itself. In general, receptors of this class respond to circulating hormonal stimuli to provoke the cell to undergo a wide array of shifts in metabolism that ultimately leads to growth and/or differentiation of the individual cells. Examples of this class of receptor include the insulin receptor (4,14) and insulin-like growth factor (IGF) receptor (15), the epidermal growth factor (EGF) receptor, the fibroblast growth factor (FGF) receptor, and the platelet derived growth factor (PDGF) receptor (5,16). Shown in Figure 2A is a schematic view of the general structure of several receptors of this class. They hold in common an extracellular domain that is responsible for binding the circulating ligand (eg, insulin), a single transmembranous sector, and most characteristically, an internal domain that has intrinsic tyrosine kinase activity. Although in normal cells less than 0.05% of all phosphorylated amino acids within proteins are phosphotyrosine, it is well recognized that this pool of phosphotyrosine is tightly regulated through the interplay of receptors possessing intrinsic tyrosine kinase activity, and tyrosine phosphatases that specifically dephosphorylate proteins that have undergone such modification (4,17).

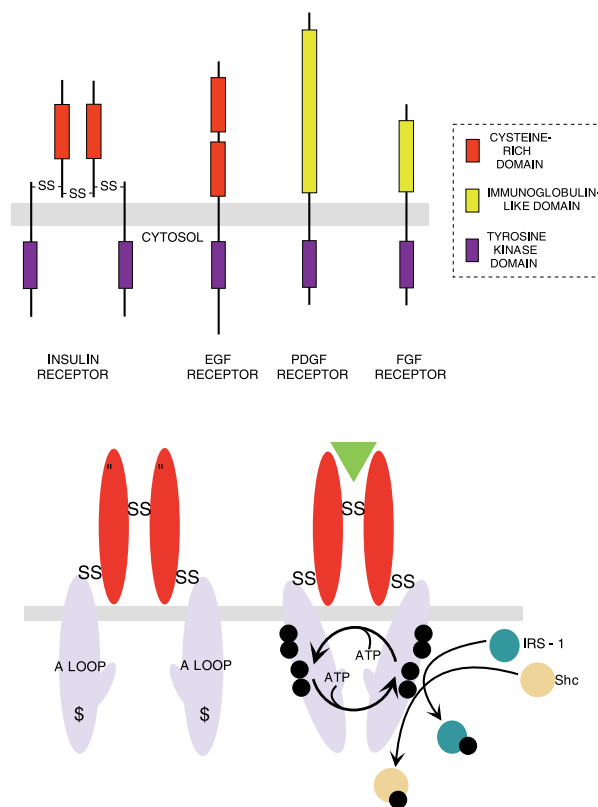


Figure 2. Models of receptors with intrinsic tyrosine kinase activity. **Top panel:** Comparison of receptor domains. **Bottom panel:** Model of the insulin receptor. As described in the text, binding of insulin (**green triangle**) results in a conformational change in the structure of the receptor that allows for trans-autophosphorylation on tyrosine residues (**black circles**). Subsequently, effector molecules with SH2 domains (IRS-1, Shc) bind to phosphotyrosine residues on the insulin receptor, and are phosphorylated.

Shown in Figure 2B is a schematic view of the insulin receptor. Much of our knowledge of the function of the various domains of the insulin receptor has been derived from analysis of naturally occurring mutations within the receptor molecule itself. As will be explored in a later article in this series, these mutations result in several forms of inherited insulin resistance. As shown, this complex exists within the membrane as a heterodimer composed of two alpha and two beta chains that are linked through disulfide bridges. The alpha subunits are external to the cell, and contain the actual insulin binding sites, and the tyrosine kinase domains are found in the beta chains within the cell interior (4). Binding of insulin to the alpha subunit results in a conformational change in the protein that is transmitted through the membrane-spanning segment to the intracellular beta subunits. These changes in the quaternary structure of the receptor activate tyrosine kinase domains in the beta subunits, which then phosphorylate multiple tyrosine residues in

the corresponding *trans* beta subunits. Subsequently, a subset of these phosphotyrosine residues serves as a docking site for signaling proteins that contain *src* homology (SH2) domains. After binding, these effector proteins are phosphorylated by the receptor on tyrosine residues, leading to their own activation. Key among these effector proteins are insulin receptor substrates (IRS 1 and IRS 2) and Shc. Subsequently, these bound proteins then activate other proteins within the cell through several signaling relays (eg, MAP kinase, PI3-kinase) that ultimately induce increased glycogen synthesis, cell growth, and insertion of the GLUT4 glucose transporter into the plasma membrane of myocytes and adipocytes (14). Termination of these insulin-provoked signals is in part achieved through the receptor-mediated endocytotic pathway described previously. Autophosphorylation of the insulin receptor triggers internalization of the receptor-ligand complex through clathrin-coated vesicles. After fusion with endosomes, insulin is released from its receptor by the acidity of the compartment, and is degraded. In addition, tyrosine phosphatases present in the endosomal membrane dephosphorylate the cytoplasmic tail of the receptor (18,19).

Other members of this family (shown in Figure 2A) undergo similar changes upon binding of their respective ligands. However, these other proteins, such as the EGF receptor, exist intrinsically within the membrane as monomers. They differ from the insulin receptor in that ligand binding to their extracellular domains initially results in a dimerization of two of these monomers. Subsequent to this, activation of the tyrosine kinase domains of the dimerized receptors leads to a cascade of signaling events generally similar to that described for the insulin receptor (5,16).

Receptors with Associated Tyrosine Kinase Activities

There exists a second subclass of enzyme-associated receptors that do not possess intrinsic tyrosine kinase activity but rather have an associated partner protein that itself has tyrosine kinase activity. Examples of this class of receptor include those responsible for binding prolactin, growth hormone, and numerous cytokines. Ligand binding to this type of receptor induces dimerization, followed by the noncovalent attachment of a nonreceptor tyrosine kinase, such as those of the *Src* family (19,20). The tyrosine kinase activity domain of this protein is thereby activated, causing phosphorylation of proteins at proximal sites in signaling pathways, in a manner similar to that described for the insulin receptor.

Receptors with Intrinsic Protein Tyrosine Phosphatase Activity

As alluded to earlier, tight control of the quantitative and qualitative aspects of phosphotyrosine formation within the cell is essential to regulation of cellular growth and

differentiation. A subclass of plasma membrane receptors have protein tyrosine phosphatases domains that play a key role in dephosphorylating phosphotyrosine residues in cellular signaling pathways. One example of such a receptor is the CD45 protein of T and B lymphocytes (21,22). When this receptor protein undergoes dimerization through cell-cell interactions (which function as nonsoluble ligands), its phosphatase domain is activated, leading to dephosphorylation of proteins within signaling cascades and by this mechanism, activation of T and B cells.

Receptors with Intrinsic Serine/Threonine Kinase Activities

A broad class of enzyme-linked receptors have been identified that have intrinsic threonine/serine kinase activity. Together these comprise the TGF- β superfamily (6,7), which includes the prototype TGF- β receptor as well as receptors that bind polypeptides that include inhibins, and bone morphogenetic and decapentaplegic proteins. Best characterized of these are the TGF- β receptors, which, in response to TGF- β , serve as a potent growth suppressors within epithelial cells (23). Structurally, this receptor exists as a single polypeptide chain with one membrane-spanning domain. The cytosolic portion of the molecule contains a domain with intrinsic serine/threonine kinase activity. Recent studies have led to the identification of cytosolic substrates for this kinase, as well as distal elements in the signaling cascade. As noted, TGF- β responses include growth inhibition and apoptosis. Mutations which disrupt function of this signaling pathway have the important property of stimulating tumor growth in various tissues, thus implicating this receptor and its signaling pathway as potential tumor suppressant elements.

RECEPTORS LINKED TO G PROTEINS

By far the largest group of plasma membrane receptors belong to the class that are linked to G proteins; to date, over 1,000 such receptors have been identified, with agonists as diverse as peptide hormones, odorants, and photons (8). Examples of such receptors include those that bind adrenaline (alpha and beta adrenergic receptors), ACTH, luteinizing hormone, parathyroid hormone, glucagon, and vasopressin (24,25). Another receptor of this class, the calcium-sensing receptor (CaR), is responsible for maintenance calcium homeostasis through its effects in parathyroid gland and the kidney (26). Mutations in the CaR, the subject of a subsequent article in this series, have recently been shown to result in three genetic diseases of calcium metabolism: familial hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcemia.

The G protein receptors have a characteristic second-

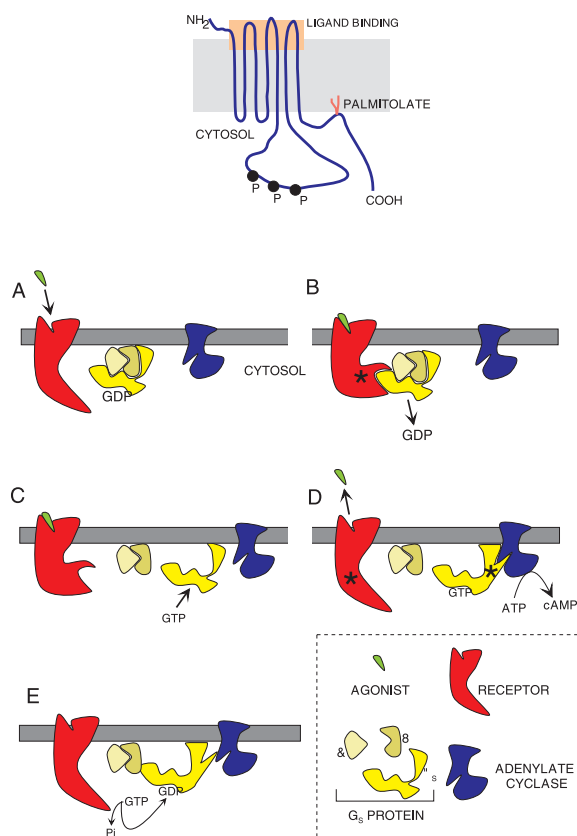


Figure 3. Top panel: Model of hypothetical G protein coupled receptor. Bottom panel: Steps in the activation and deactivation of a heterotrimeric G protein, as described in the text.

ary structure (Figure 3) that includes an extracellular amino terminus, seven transmembranous sectors, and a cytosolic carboxyl terminus (27–29). This seven-pass “serpentine” transmembranous structure has been highly conserved from an evolutionary standpoint, and can be traced phylogenetically to the light driven proton pump of bacteriorhodopsin (1) whose vertebrate counterpart, rhodopsin, functions as the retinal light-sensing protein (30). Additional structural features of some G protein linked receptors include sites in the carboxyl terminus of the molecule that, when phosphorylated, inactivate the receptor as a means of desensitizing the system to further agonist stimulation (31,32).

As a class, these receptors utilize G proteins to activate their effector pathways. Once agonist binds to the extracellular face of the receptor, there is a resulting change in the conformation of the cytosolic portion of the molecule that permits binding of a G protein complex. The latter consists of three subunits, termed alpha, beta and gamma. Under basal conditions, one molecule of GDP is bound to the alpha subunit. Association of the G protein complex with its receptor results in release of GDP from the alpha subunit. Subsequently, a molecule of GTP binds to the alpha subunit, provoking release of the hetero-

meric G protein complex from its receptor. The released heterotrimeric G protein dissociates into an isolated alpha subunit and a gamma-beta heterodimer. The alpha subunit then diffuses laterally on the cytosolic face of the plasma membrane and activates (or inhibits) one, or several, effector molecules, which include adenylyl cyclases, phospholipases, phosphodiesterases, PI-3 kinases and ion channels. These effector molecules, in turn, activate one, or several, signaling pathways that amplify the agonist signal, and generate the cellular responses characteristic of the agonist (8). Recently, it has become evident that the released beta-gamma heterodimer is also a regulator of numerous effector systems, and it likely has a range of functions similar in breadth to that of the isolated alpha subunit. Termination of the signaling activity of the isolated alpha subunit occurs when its molecule of GTP is hydrolyzed to GDP and Pi. Once this occurs, the alpha subunit reassembles with the beta-gamma pair to result in an inert, heterotrimeric complex that awaits a repeat of the activation cycle. Intrinsically, the specific activity of this GTPase is quite low, which potentially results in a prolonged signaling period. However, a group of regulatory proteins, termed GTPase activating proteins (GAPs), directly interact with the isolated alpha subunit to accelerate the hydrolysis of GTP, thereby regulating the agonist-induced signaling event.

A single cell typically has multiple different G protein coupled receptors on its plasma membrane. In such a setting, the maintenance of specificity in agonist function requires selective activation of the appropriate signaling and effector pathways. The compartmentalization of signaling by G protein coupled receptors is achieved through polymorphic diversity in activation pathways. This includes extensive isoform variation at the level of the receptors themselves. As an example, at least 5 isoforms of dopamine receptors have been identified that vary in their responses to agonists and antagonist, as well as in their effector system interfaces (33). Second, there exist multiple forms of the alpha, beta and gamma subunits, which have 16, 5, and 12 isoforms, respectively (8). These isoforms differ not only in their affinities for different receptors and signaling molecules, but also in their qualitative effects (activation versus inhibition) on their target effector protein. Additional diversity of trimeric G proteins may arise from the numerous possible combinations of the multiple isoforms of the alpha, beta and gamma subunits. Third, there are multiple isoforms of effector molecules, such as adenylyl cyclase, which differ in their responses to alpha subunits, and beta-gamma pairs of G proteins.

ION CHANNEL RECEPTORS

Although some ion channels are regulated by G proteins other plasma membrane channels function as receptor

molecules themselves. Examples of such channel type receptors include GABA-gated chloride channels, serotonin-gated cation channels, and the acetylcholine receptor, which functions as a sodium channel, and triggers action potential generation in muscle cells (8,10). These channel-type receptors have in common a specific ligand binding site on the extracellular face of the channel protein and binding of ligand modulates the channel conductance through an allosteric effect. In the case of the acetylcholine receptor, binding of agonist opens the channel, whereas GABA causes closure of the chloride conductance in its channel receptor. In both instances, the resulting change in membrane potential, itself, serves as the initial signal effector.

The acetylcholine receptor of neuromuscular junctions is a well-characterized channel-type receptor. The protein is a hetero-oligomer, composed of four different subunits, α , β , γ , and δ , at a stoichiometry of 2:1:1:1. Each of these subunits has four transmembranous sectors, for a total of 20 per receptor molecule. Current models suggest that one transmembranous helix from each of the five subunits contributes to the actual ion channel. There are two acetylcholine binding sites per channel; these binding sites are likely present on the alpha subunits. Acetylcholine, released from the nerve terminal, accumulates briefly within the synaptic cleft at a relatively high concentration (10^{-4} M) and binds to resident acetylcholine receptors on the plasma membrane of the muscle cell. If both binding sites are occupied, the channel opens for about 1 millisecond, during which time about 30,000 sodium ions pass, leading to initiation of an action potential. After spontaneous closure of the channel, the two molecules of acetylcholine are released into the cleft and are hydrolyzed by acetylcholinesterase. In addition to binding acetylcholine, the alpha subunits of the receptor are the targets of inhibitory antibodies in the autoimmune disorder, myasthenia gravis, a subject to be covered in a subsequent article in this series (10).

INTRACELLULAR RECEPTORS

Although all classes of receptors described above are integral membrane proteins that reside on the plasma membranes of cells, many receptors that bind circulating hormones are soluble proteins that are localized to the cytosol, or nucleus. Together, these receptors are members of the steroid hormone receptor superfamily (11,12). In addition to cortisol and steroid sex hormones, receptors within this category bind thyroid hormone, 1,25 dihydroxyvitamin D₃, and retinoids (34,35). Direct molecular approaches have also led to the identification of homologous proteins, termed orphan receptors, that at present have no identifiable ligand.

Members of this superfamily of receptors function as

transcription regulatory elements; reflecting this, they share a highly conserved DNA binding motif that contains two zinc finger domains. Some, such as the cortisol receptor, are found predominantly in the cytosol, and enter the nucleus after the steroid is bound. In other instances (eg, the estrogen receptor), the receptor protein is constitutively situated in the nucleus and is bound to DNA. In both cases, the receptors are usually inactive in the absence of ligand, and exist in a complex with an inhibitory protein. Ligand binding results in dimerization of the receptor and release of the associated inhibitory protein. In conjunction with constitutive transcription factors, the receptor-ligand complex then induces transcription of its target genes. Within 30 minutes of binding ligand, these receptors initiate a primary response leading to the synthesis of a group of proteins that are transcription regulatory elements themselves. Subsequently, these factors initiate a second wave of transcription, leading to the translation of proteins that produce the cellular responses that typify the action of the specific ligand. Beyond this generality, it appears that in some circumstances these receptors can activate transcription in the absence of ligand. In these instances, the receptor protein is activated by growth factors that stimulate kinase pathways, leading to phosphorylation of the receptor (33–35).

SUMMARY

Receptor proteins are responsible for the selective action of a multitude of regulatory factors that include circulating peptide and steroid hormones, as well as odorants, photons, and toxins. Specificity in the action of these ligands owes most directly to the receptor proteins themselves, which, as a result of their localization to discrete populations of cells, restrict responses to their target tissues. Although the structure of receptors varies considerably between their classes, key functions of these proteins are universal. These include structural specificity in their ligand binding sites, as well as conformational changes that result from ligand binding. The latter serves, directly or indirectly, to modulate the activity of a specific effector, which in turn regulates a signaling pathway leading to phenotypic changes that typify the ligand. Genetic or acquired modifications of receptor proteins result in a diverse set of diseases that will be discussed in subsequent articles in this series.

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