1
Introduction

> The beauty of reductionism is that it gives you something to do next.
>
> *Steve Jones [1]*

Biological processes require communication between cells and between individuals. In all kinds of living organisms, this communication begins at the molecular level. Small **signaling molecules** (proteins, amino acids, steroids, and other substances) are the messages that pass from one cell to the next; large protein **receptors** are the receivers of the message. Receptors bind the smaller molecules much as a lock receives a key or a glove receives a hand [2]. Other proteins in the cell membrane associated with the receptors convey the message to the interior of the cell.

Very few biochemical or physiological functions in our bodies are not somehow touched by these molecules or by the process of cellular communication. Here are some examples of how receptors are involved in a variety of biological processes:

- Sperm and egg meet, recognize each other, and bind by a receptor mechanism.
- Embryos develop by cell communication: one cell releases a **hormone** that binds to a receptor on another cell, and the second cell changes its shape and function, initiating the process of **differentiation.**
- Hormone-like **neurotransmitters** are released from one cell (a nerve) and bind to receptors on the surface of a nearby cell (another nerve or a muscle) to cause thought or movement.
- The digestive system propels food and releases enzymes according to the binding of hormones to cells lining the digestive tract.
- Immune system cells contain on their surfaces receptors that are able to recognize foreign proteins and attack invading cells.
- Diseases often act by subverting normal receptor function.

This introductory chapter covers general concepts of communication and how chemical communication compares with human communication; how evolution applies to receptor molecules; and how a pure chemical entity such as a receptor can initiate such large-scale functions as thought.

1.1
Receptors and Signaling

1.1.1
General Aspects of Signaling

Signaling is the means by which a cell knows what is happening in its surroundings, and is also the method by which one cell instructs nearby cells to alter their behavior. Organismal cell signaling involves molecular interactions, but the biological mechanisms of signaling are analogous to the ones humans use for verbal communication.

1.1.2
Verbal and Physiological Signals

Any sort of signaling requires that the sender and receiver are capable of interpreting the signals in the same way [3]:

- The sender must relay a characteristic signal, and it must be received by a characteristic device;
- The signal is *arbitrary:* it bears no real relation to the process it starts but is simply a way of obtaining a response in the receiver;
- The signal is *simpler* than the process it sets in motion.

These rules are easily understood in terms of human communication:

- The signals are the words of the language, and the receiver is the hearing/thinking/acting apparatus of another person;

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- Each language uses different words, yet all people can express the same thoughts.
- Any word (e.g., HELP) evokes in its hearer a set of thoughts or behaviors that are much more complex than the word itself.

The units of cellular communication abide by these same rules:

- The correct signal is the **drug** or hormone, the correct receiver is the **cell surface receptor** or **nuclear receptor**.
- It is arbitrary that one amino acid (e.g., glutamic acid) is an excitatory **transmitter** in the nervous system, whereas another amino acid (e.g., glycine) is an inhibitory transmitter.
- The binding of a single transmitter molecule to its receptor is adequate to start a cascade of intracellular events that amplifies the signal into a complex biochemical response.

In addition to these constraints, three more generally apply to biological communication:

- The receptor must be present on the correct **tissue**, it must be **selective** or specific to the hormone, and the receptor must *not* be present in tissues where the response is not desired; thus, the timing of the message must be coordinated with the presence of the receptor for that message.
- The signal must always mean the same thing to a particular receptor–**effector** mechanism.
- Some transmitters act on more than one type of receptor, often activating antagonistic cellular processes.

The analogies drawn between human communication and chemical communication are symbolic, yet the correspondence between the two systems is being strengthened as we find more instances where human interactions are being found to be at least partly chemical (e.g., the importance of **pheromone**-like substances in human behavior [4]).

1.1.3 Criteria for Recognizing Transmitters and Receptors

This book refers to signaling molecules in several ways. The most general term is **ligand**, which means any molecule that binds to a receptor. A ligand that activates its receptor is called an **agonist**. Hormones, transmitters, and pheromones are all agonists, and are naturally produced by organisms for signaling.

1.1.4 Agonists

The substances that serve as agonists are often also important as metabolic molecules within the cell. Thus, simply showing that a cell produces acetylcholine, for example, does not demonstrate its role as a transmitter. For a substance to be accepted as a specific transmitter or hormone, it must be shown to: [5]

- be synthesized, stored, and released from the proper type of cell (e.g., neuron or **endocrine** cell);
- have a specific mechanism for removal from the extracellular space near the target cell;
- be effective as an agonist if added to the target cell by experimenters.

1.1.5 Receptors

Cells can be activated by processes other than receptor mechanisms. To be accepted as a receptor mechanism, a process must be shown to [6]

- be activated by one or only a few substances;
- bind these substances with high **affinity**;
- be able to transmit the binding event to the cell interior.

These criteria for identifying receptors are not just for convenience; each has its basis in receptor structure, and later chapters show how these criteria are derived from, and actually define, the molecular mechanisms by which receptors operate.

1.1.6 Receptor–Enzyme Similarities

Enzymes are familiar proteins: they have **active sites** at which small **substrate** molecules bind and are converted to **products**. The relation between a receptor and its agonist is quite similar, at least at the binding step, to the action of enzymes: the receptor binds the agonist with high **affinity** because of the match between the shape and electric charge distribution of both molecules. The act of binding alters the shape of the receptor at another location; this change in shape is transmitted to other cellular proteins, thus stimulating further cellular processes.

As useful as the enzyme analogy is, however, enzyme action is unlike the receptor mechanism in some ways:

Table 1.1 Locations and properties of the four receptor superfamilies.

	Ion channel receptors	G-protein-coupled receptors	Receptor tyrosine kinases	Nuclear receptors
Location	Plasma membrane	Plasma membrane	Plasma membrane	Nucleus
Effector	Ion channel	Enzyme or ion channel	Enzyme	Regulation of gene action
Time scale	Milliseconds – seconds	Seconds – minutes	Minutes – hours	Hours – days
Examples	Nicotinic receptors	Adrenoceptors	Insulin receptors	Steroid receptors

- A receptor-binding event has no "product" because the agonist is unaltered by its interaction with the receptor.
- The receptor – agonist complex has an additional role after binding: the conversion of the binding signal to an intracellular event, such as enzyme activation or gene **transcription**.

Enzymes are important intracellular biochemical regulators; receptors are important regulators at the interface of the cell. Because of this location, they have a crucial role as molecular guardians, controlling the initial encounters between cells and chemicals in their environments.

1.2 Types of Receptors and Hormones

1.2.1 Receptor Superfamilies

A protein superfamily is a group of proteins that share structure, sequence, and functional features suggesting they are derived from the same common ancestral protein [5]. At present, researchers recognize four large superfamilies[1] of receptors: three reside in the cell membrane and one remains within the cytoplasm of the cell. Almost a thousand types of cell surface receptors belong to a single superfamily, the G-protein-coupled receptors. Their DNA thus comprises about 5% of all human genes. Another large superfamily of receptors is the fast ion channels that mediate neurotransmission in the central nervous system and skeletal muscles. A small superfamily, the receptor kinases, mediates metabolic, developmental, and immunological processes (Chapter 8). Also present in small quantities in the cytoplasm of the cell are the nuclear receptors that control transcription of new proteins. Table 1.1 summarizes the properties of the four superfamilies or receptors [7].

These four types are easily distinguished by shape, they each have characteristic agonists, and each causes characteristic intracellular changes. Figure 1.1 shows general structures of the four superfamilies.

The first superfamily (Chapter 6) consists of **ion channels** such as the nerve Na^+ channel that is activated by acetylcholine. These receptors consist of several protein chains held together in a ring. Each protein has four transmembrane regions. Together the separate chains form the pore through which the Na^+ ion moves when the agonist binds. The inward flux of Na^+ **depolarizes** the cell, causing it to generate an action potential.

The second superfamily (Chapter 7) consists of receptors such as the one for the neurotransmitter **norepinephrine** (NE) on heart muscle cells. This receptor has seven transmembrane regions, meaning the single receptor molecule passes through the cell membrane seven times and has both intracellular and extracellular regions. When a transmitter such as NE binds, it causes the receptor to activate a multiprotein assemblage in the membrane that produces an intracellular **second messenger** (such as **cyclic adenosine monophosphate (cAMP)**) that activates the cell by altering the level of phosphorylation of cellular enzymes. In the heart muscle, one effect of NE is to increase the strength of the heartbeat.

The third superfamily (Chapter 8) consists of the **receptor kinases**, growth factor receptors for substances such as the proteins insulin and **epidermal growth factor**. These receptors have a single transmembrane region, and their cytoplasmic end is an enzyme – a kinase. The binding of the hormone to the outer portion activates the kinase to phosphorylate cellular enzymes that regulate nutrient transport and cell division.

The fourth superfamily (Chapter 9) consists of the **intracellular receptors**, the proteins that bind

1 Several terms are used in receptor literature to denote classes of receptors: *superfamily, family, class, group, and clan*, often inconsistently. We use the term *superfamily* to refer only to the four major groups of receptors, and use the other terms in order: within each superfamily are found *families* (e.g., the several types of ion channels); within each family are found *classes* (e.g., the types of Ca^{2+} channel). *Group* will be used informally and sparingly, *clan* not at all.

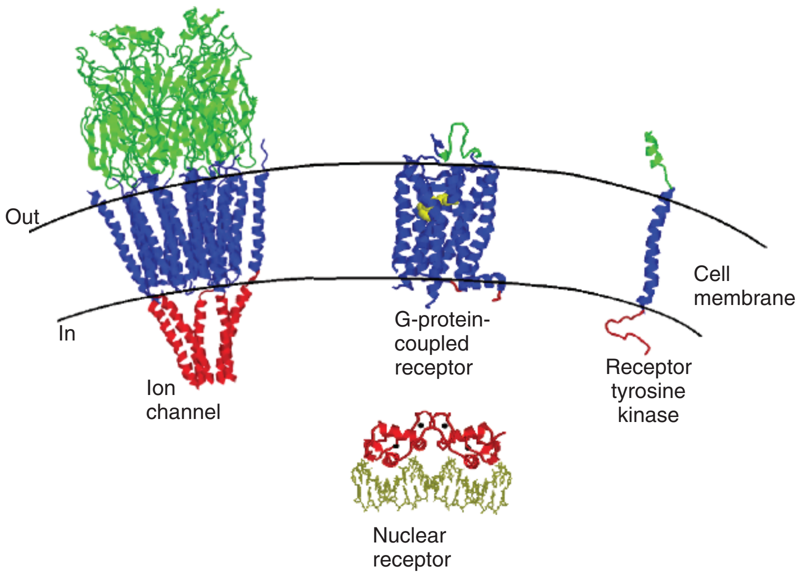

Figure 1.1 Overview of the four major receptor types. (A) Ion channel with extracellular **domain** labeled in red and transmembrane chains labeled in green; (B) G-protein-coupled receptor with extracellular domains labeled in red, seven transmembrane domains labeled in green; (C) receptor tyrosine kinase with transmembrane domain labeled in green, extracellular regions in red, and intracellular regions in blue. Black lines represent lipid bilayer; and (D) nucleus (dashed line) with nuclear receptors labeled in blue dimerizing on a DNA template labeled in black. Images were created using Rasmol [8] from PDB ID [9], PDB ID 1F88 [10], PDB ID [11], and PDB ID [12].

steroids, thyroid hormone, and certain vitamins. These fat-soluble ligands diffuse through the cell membrane to the interior of the cell, where they bind to and activate receptor proteins that enhance synthesis of new proteins within the cell.

Receptors are involved in cellular processes, such as metabolism and ionic changes, as well as cell division, growth, and protein synthesis. This book also covers receptor actions at a higher, organismal level. Embryonic development (Chapter 11), disease (Chapter 12), and the activities of the mind (Chapter 13) all involve integration of many physiological systems, all bound by the same receptor process as cell–cell communication.

All classes of receptors are encoded by genes within each cell. Genes for receptors are also subject to mutation and evolve by natural selection. As a consequence, receptors will change over time, allowing us to draw evolutionary inferences from the present phylogenetic distribution of genes for families of receptor molecules. The "fossil record" of proteins is thus found not in the rocks of the world but in the diversity of present-day organisms. The four superfamilies of receptors described are all widespread in eukaryotes. Some superfamilies are also present in prokaryotes, and the study of their distribution among all organisms (Chapter 14) gives researchers an understanding of their functions and role in organismal adaptations.

The relationships among protein families suggest that their genes have mutated, changed location, and duplicated many times, each time allowing the production of new protein molecules with similar functions. These similarities indicate further that protein function can change over time, and that new proteins with completely different functions can arise from gene mutations. This seems to be how some receptors arose, and how the families of receptors have changed.

1.3 Receptors Are the Chemical Expression of Reality

Because receptors are at the interface between cells and their environments, they are the first cellular units to receive environmental information and provide crucial information about the surroundings. For example, animals know that nighttime is the time to sleep, even though their brains have no way of directly sensing the light or dark. Visual information from the eyes goes to the pineal gland, which produces the hormone melatonin in inverse proportion to the amount of ambient light. Melatonin is therefore the *chemical expression of* darkness [13].

In an analogous manner, other hormone and receptor systems give information about the food taken in by organisms. Insulin is produced in the pancreas following a meal when blood glucose levels rise. Insulin is therefore the *chemical expression of plenty.* When food is scarce, the adrenal gland produces the steroid cortisol as a means of liberating glucose from storage forms in cells. Cortisol can be seen as the *chemical expression of starvation.* As melatonin, insulin, and cortisol all act on cellular receptors, we view receptor mechanisms as an important way that organisms have of knowing what reality is.

As the foregoing suggests, receptors are complex, as are their interactions with cellular processes. However, we hope that this complexity will be made comprehensible by the approach we are taking: the thousands of different receptors fall into only four fundamental superfamilies; each has a unique structure and a unique way of activating the cell, so it is possible to identify an unfamiliar receptor if one knows only a few things about it. Knowledge of receptor function illuminates the many interactions among proteins in the body and gives researchers important information on higher level functions of cell physiology (e.g., the normal workings of the mind or the aberrant interactions involved in disease states).

The book is divided into three parts: first is a general discussion of cell membranes, proteins, hormone types, and receptor theory.[2] Next follows one chapter on each of the four receptor types. Finally, several chapters outline receptor-mediated biological processes such as embryonic development, disease, mechanisms of the mind, and the evolution of these remarkable molecules.

Pharmacology texts generally focus on hormones and the kinetics of drug actions. We have written this book for students who wish to become more familiar with receptors themselves: the mechanisms by which they act, the sorts of processes they direct, and their evolution as molecules. It is meant for students at the advanced undergraduate and early graduate levels and requires an understanding of fundamental chemical and biological principles, a general knowledge of evolutionary thought, and a grasp of physiological interactions – all concepts that are part of any good general biology course. The text builds on these ideas to help students form a more complex understanding of pharmacology and cellular biochemistry.

Evolutionary inferences provide information that allows the study of receptors to be not only exciting and useful but also conceptually possible: despite the bewildering array of cell surface receptor types, they fall into just four major categories and interact with only a few dozen other membrane effector proteins that transmit the binding event into a biochemical process. Thus, genetic relationships among receptors are relatively simple, and their use of similar biochemical mechanisms shows that the important problems of cell-to-cell signaling have needed to be solved only a few times in evolution.

We wrote the book because in our teaching and research we see the importance of receptor mechanisms and intracellular signaling across all kingdoms of organisms and in many types of cellular processes. Even so, it is difficult to find a book that gives them complete coverage (structure, mechanism of action, evolutionary history) without being written specifically for professionals. The two unifying themes of the book are (i) the receptor concept itself: the idea that biological communication is involved in nearly all the activities of living things, and that receptor function is the mechanism of that communication and (ii) the role of natural selection and evolution in shaping receptor structure and function. We hope that this book will give a clear idea of the roles that hormones and their receptors play in our lives, from the reactions of individual cells to the behavior of whole organisms.

2 The term *theory* is often used by mistake in place of *hypothesis.* In proper usage, a theory is a hypothesis that has been tested and promoted to the level of widespread acceptance as a major concept in science. It is unfortunate that scientists themselves often misuse *theory* to mean *hypothesis*, as in "I have a theory about that" and non-scientists often pounce on this misuse to denigrate science, as in "evolution is only a theory." In this book, we restrict the use of the term *theory* to major scientific concepts, such as the *theory of evolution*, or *cell theory*, or *receptor theory.* All three of these ideas have been rigorously tested; they are no longer hypothetical, but have become key concepts in biological thinking. Other concepts, still provisional, are called *hypotheses*.