

## Contents

	<b>Acknowledgment</b>	XIII				
	<b>Part I</b>	<b>Introduction</b>	1			
1	<b>Introduction</b>	3	3.1.2.3	A New View of Membrane Proteins	19	
1.1	Receptors and Signaling	3	3.1.2.4	The Modern Concept of Membranes – the Fluid Mosaic Model	19	
1.1.1	General Aspects of Signaling	3	3.1.3	Membrane Components	19	
1.1.2	Verbal and Physiological Signals	3	3.1.3.1	Membrane Lipids	19	
1.1.3	Criteria for Recognizing Transmitters and Receptors	4	3.1.3.2	Asymmetry and Heterogeneity in Membrane Lipids	20	
1.1.4	Agonists	4	3.1.3.3	Membrane Construction and Insertion of Proteins	20	
1.1.5	Receptors	4	3.2	The Nature and Function of Proteins	21	
1.1.6	Receptor–Enzyme Similarities	4	3.2.1	Linear and Three-Dimensional Structures	22	
1.2	Types of Receptors and Hormones	5	3.2.2	Primary Structure	22	
1.2.1	Receptor Superfamilies	5	3.2.3	Secondary Structure	23	
1.3	Receptors Are the Chemical Expression of Reality	6	3.2.4	Tertiary Structure	24	
			3.2.5	Protein Domains	25	
			3.2.6	Proteomics	25	
2	<b>The Origins of Chemical Thinking</b>	9	4	<b>Hormones as First Messengers</b>	27	
2.1	Overview of Early Pharmacological History	9	4.1	Hormones and Cellular Communication	27	
2.1.1	The Development of a Chemical Hypothesis	9	4.1.1	Discovery of Hormones	27	
2.1.2	Chemical Structure and Drug Action	10	4.2	Types of Hormones	27	
2.1.3	The Site of Drug Action	10	4.2.1	Pheromones for Signaling between Individuals	28	
2.2	Modern Pharmacology	10	4.2.2	Archaea and Bacteria	28	
2.2.1	Langley and Ehrlich: the Origins of the Receptor Concept	10	4.2.3	Eukaryotes	29	
2.2.2	Maturation of the Receptor Concept	13	4.2.3.1	Chromalveolates	29	
2.3	Phylogenetics of Signaling	13	4.2.3.2	Unikonts – Amoebozoa, Fungi, Animals	29	
2.3.1	The First Communicators	13	4.2.3.3	Invertebrate Pheromones	31	
			4.2.3.4	Vertebrate Pheromones	31	
	<b>Part II</b>	<b>Fundamentals</b>	15	4.3	Vertebrate Hormones and Transmitters	31
3	<b>Membranes and Proteins</b>	17	4.3.1	Peptide and Non-Peptide Agonists	31	
3.1	Membranes	17	4.3.1.1	Peptides	31	
3.1.1	The Cytoplasmic Membrane – the Importance of Cell Membranes	17	4.3.1.2	Non-peptides	31	
3.1.2	History of Membrane Models	17	4.3.2	Peptide Hormones of the G-Protein-Coupled Receptors	32	
3.1.2.1	The Roles of Proteins in Membranes	18	4.3.2.1	Hypothalamic-Pituitary Axis	32	
3.1.2.2	Challenges to the Danielli–Davson Model	19				

## VIII Contents

4.3.2.2	The Anterior Pituitary Trophic Hormones	34	5.3.2.2	The Ternary Complex Model	53
4.3.3	Other Neural Peptides	35	5.3.2.3	Protean Agonism	54
4.3.3.1	Opioids	35	5.3.2.4	Cubic Ternary Complex (CTC) Model	55
4.3.3.2	Non-Opioid Transmitter Peptides	36	5.3.3	Summary of Model States	55
4.3.4	Peptides from Non-Neural Sources	36	5.4	Visualizing Receptor Structure and Function	55
4.3.4.1	Digestive Tract Hormones	36	5.4.1	Determination of Receptor $K_d$	55
4.3.4.2	Hormones from Vascular Tissue	38	5.4.1.1	Schild Analysis	56
4.3.4.3	Hormones from the Blood	38	5.4.2	Visualizing Ligand Binding	57
4.3.4.4	Peptide Hormones from Reproductive Tissues	39	5.4.2.1	Receptor Preparation	58
4.3.4.5	Hormones from Other Tissues	39	5.4.2.2	Equilibrium Binding Studies	58
4.3.5	Non-Peptides Acting on G-Protein-Coupled Receptors	39	5.4.2.3	Competition Studies	58
4.3.5.1	Transmitters Derived from Amino Acids	39	5.4.3	X-ray Crystallography of Native and Agonist-Bound Receptors	59
4.3.5.2	Transmitters Derived from Nucleotides	40	5.4.4	Probe Tagging (Fluorescent and Photoaffinity)	60
4.3.5.3	Transmitters Derived from Membrane Lipids – Prostaglandins and Cannabinoids	41	5.5	Proteomics Approaches to Receptor Efficacy	60
4.3.6	Transmitters of the Ion Channels	41	5.6	Physical Factors Affecting Receptor Binding	61
4.3.7	Hormones of the Receptor Kinases – Growth Factor Receptors	43	5.6.1	Temperature	61
4.3.7.1	Insulin	43	5.6.2	Relation of Agonist Affinity and Efficacy to Distance Traveled Following Release	61
4.3.7.2	Insulin-Like Growth Factors	43			
4.3.7.3	Natriuretic Peptides	43			
4.3.7.4	Peptide Signal Molecules Important in Embryogenesis	43			
4.3.7.5	Pituitary Gland		<b>6</b>	<b>Part III Receptor Types and Function</b>	<b>63</b>
	Hormones – Somatotropin and Prolactin	43			
4.3.8	Hormones of the Nuclear Receptors	44	6.1	<b>Transduction I: Ion Channels and Transporters</b>	<b>65</b>
4.3.8.1	Steroids	44	6.2	Introduction	65
4.3.8.2	Non-Steroid Nuclear Hormones	46	6.2.1	Family Relationships	65
4.4	Analgesics and Venoms as Receptor Ligands	46	6.2.2	Small Molecule Channels	66
			6.2.2.1	Osmotic and Stretch Detectors	66
<b>5</b>	<b>Receptor Theory</b>	<b>47</b>	6.2.2.2	Voltage-Gated Cation Channels	66
5.1	The Materialization of Receptors	47		History of Studies on Voltage-Gated Channels	66
5.2	Receptor Mechanisms	47		Structure and Physiology of Ion Channels	68
5.2.1	Binding of Agonist to Receptor	48	6.2.3	Potassium Channels	68
5.2.1.1	Bonds	48	6.2.4	Sodium Channels	70
5.3	Binding Theory	49	6.2.4.1	Bacterial $\text{Na}^+$ Channels	70
5.3.1	Early Approaches to Understanding Receptor Action	49	6.2.4.2	Vertebrate $\text{Na}^+$ Channels	70
5.3.1.1	The Occupancy Model	49	6.2.5	Calcium Channels	71
5.3.1.2	Processes That Follow Receptor Activation	52	6.2.6	Non-Voltage-Gated Cation Channels – Transient Receptor Potential (TRP) Channels	72
5.3.1.3	Efficacy and Spare Receptors	52	6.3	Transporters	73
5.3.2	Modern Approaches to Receptor Theory	52	6.3.1	Pumps and Facilitated Diffusion	73
5.3.2.1	The Two-State Model	52	6.3.1.1	The SLC Proteins	73
			6.3.1.2	The Pumps	74
			6.3.2	The Chloride Channel	76

6.4	Major Intrinsic Proteins 76	7.4.1.1	The $\alpha$ Subfamily 99
6.4.1	Water Channels 76	7.4.1.2	The $\beta$ Subfamily 102
6.4.2	Glycerol Transporters 77	7.4.1.3	The $\gamma$ Subfamily 102
6.5	Ligand-Gated Ion Channels 77	7.4.1.4	The $\delta$ Subfamily 104
6.5.1	Four-TM Domains – the Cys-Loop Receptors 77	7.4.2	Family B – Secretin-Like 104
6.5.1.1	The Four-TM Channels for Cations 78	7.4.3	Family C – Metabotropic Glutamate and Sweet/Umami Taste Receptors 104
6.5.1.2	The Four-TM Channels for Anions 80	7.4.3.1	Taste 1 Receptors (T1Rs) 105
6.5.2	Three-TM Domains – Ionotropic Glutamate Receptors 82	7.4.3.2	Calcium-Sensing Receptors 106
6.5.2.1	Glutamate-Gated Channels 82	7.4.4	Family D – Adhesion Receptors 106
6.5.2.2	N-Methyl-D-aspartate (NMDA) Receptor 82	7.4.5	Family F – Frizzled-Smoothened Receptors 106
6.5.2.3	Non-NMDA Receptors 82	7.4.6	Family E – Cyclic AMP Receptors 106
6.5.3	Two-TM Domains – ATP-Gated Receptors (P2X) 82	7.4.7	Other G-Protein-Coupled Receptor Types in Eukaryotes 106
7	<b>Transduction II: G-Protein-Coupled Receptors 85</b>	7.4.7.1	Yeast Mating Pheromone Receptors 106
7.1	Introduction 85	7.4.7.2	Insect Taste Receptors 106
7.1.1	Receptor Function 86	7.4.7.3	Nematode Chemoreceptors 106
7.1.2	Sensory Transduction 87	8	<b>Transduction III: Receptor Kinases and Immunoglobulins 107</b>
7.1.2.1	Chemoreception in Non-Mammals 87	8.1	Protein Kinases 107
7.1.2.2	Chemoreception in Mammals 87	8.2	Receptors for Cell Division and Metabolism 108
7.2	Families of G-Protein-Coupled Receptors 89	8.2.1	Overview of Family Members 108
7.3	Transduction Mechanisms 89	8.2.2	Overall Functions of RTK 108
7.3.1	Discovery of Receptor Control of Metabolism – Cyclic AMP and G Proteins 89	8.2.2.1	Extracellular Domains 108
7.3.1.1	Components of the Process of Metabolic Activation 89	8.2.2.2	Intracellular Domains 109
7.3.1.2	Discovery of Cyclic AMP 90	8.2.3	Receptor Tyrosine Kinase Subfamilies 110
7.3.1.3	Discovery of G Proteins 90	8.2.3.1	EGF Receptor Subfamily 111
7.3.2	Actions of G Proteins 91	8.2.3.2	Insulin Receptor Subfamily 111
7.3.2.1	G-Alpha Proteins 92	8.2.3.3	FGF and PDGF Receptor Subfamilies 111
7.3.2.2	Roles of the Beta and Gamma Subunits 95	8.2.3.4	NGF Receptor Subfamily 111
7.3.3	Proteins That Enhance (GEF) or Inhibit (GAP) GTP Binding 96	8.3	Receptor Serine/Threonine Kinases 112
7.3.3.1	GEF Protein 96	8.3.1	Transforming Growth Factor-Beta (TGF- $\beta$ ) Receptor 112
7.3.3.2	GAP Protein 96	8.4	The Guanylyl Cyclase Receptor Subfamily – Natriuretic Peptide Receptors 112
7.3.4	Signal Amplification 97	8.5	Non-Kinase Molecules – LDL Receptors 113
7.3.5	Signal Cessation – Several Processes Decrease Receptor Activity 97	8.5.1	Cholesterol Transport 113
7.3.6	Interactions between Receptors and G Proteins 97	8.5.2	The Low-Density Lipoprotein (LDL) Receptor 114
7.3.7	Summary of Actions of GPCRs: Agonists, Receptors, G Proteins, and Signaling Cascades 98	8.5.2.1	Clathrin-Coated Pits 114
7.4	The Major Families of G Protein-Coupled Receptors 99	8.6	Cell–Cell Contact Signaling 115
7.4.1	Family A – Rhodopsin-Like 99	8.6.1	Notch–Delta Signaling 115
		8.7	Immune System Receptors, Antibodies, and Cytokines 115
		8.7.1	The Innate Immune Responses 115

8.7.2	The Cells and Molecules of the Adaptive Immune System	116	10.3.2.1	Other G-Protein-Like Transducers – Ras	139
8.7.3	T-Cell Receptors and Immunoglobulins	116	10.3.2.2	Other G-Protein-Like Transducers – Ran	139
8.7.4	Cell-Surface Molecules	117	10.3.3	Cell Aggregation and Development	140
8.7.4.1	The MHC Proteins	117	10.3.3.1	Coaggregation in Bacteria	140
8.7.4.2	Receptors of the B and T Cells	118	10.3.3.2	Aggregation in Eukaryotes	140
10.3.3.3			10.3.3.3	The Molecules of Cell Adhesion	141
<b>9</b>	<b>Transduction IV: Nuclear Receptors</b>	<b>121</b>	10.4	Complexity in Cross Talk – Roles of PIP3, Akt, and PDK1	141
9.1	Introduction	121	10.4.1	Signaling Cascades Using PIP3	142
9.2	Genomic Actions of Nuclear Receptors	122	10.4.2	Integrins	144
9.2.1	Families of Nuclear Receptors	122	10.4.3	Receptor Tyrosine Kinases	144
9.2.2	Transcription Control	122	10.4.4	Cytokine Receptors and the JAK/STAT Proteins	144
9.2.3	Constitutively Active Nuclear Receptors	122	10.4.5	Combined Cellular Signaling – GPCR and RTK Actions	144
9.2.4	Liganded Receptors	122	10.5	Role in Cancer	144
9.2.5	History of Steroid Receptor Studies	123	10.5.1	Constitutive versus Inducible Activation	144
9.2.6	Receptor Structure	123	10.5.2	Cancer Pathways	146
9.2.7	The Ligand-Binding Module	124	10.6	Signaling Mediated by Gas Molecules	146
9.2.8	The DNA-Binding Module	125	10.6.1	Carbon Monoxide	147
9.2.9	Specific Nuclear Actions	125	10.6.2	Nitric Oxide	147
9.2.9.1	Family 1 – Thyroid Hormone and Vitamins A and D Receptors	125	10.6.3	Hydrogen Sulfide	148
9.2.9.2	Family 2 – Fatty Acid (HNF4) and Retinoic X Receptors (RXR)	127	<b>11</b>	<b>Cellular Interactions in Development</b>	<b>149</b>
9.2.9.3	Family 3 – Steroid Receptors for Estrogens, Androgens, Progestogens, Mineralocorticoids, and Glucocorticoids	128	11.1	Introduction	149
9.3	Actions of Receptor Antagonists	129	11.2	The Origins of Multicellularity	150
9.4	Non-Traditional Actions of Steroid-Like Hormones and Their Receptors	130	11.2.1	Multicellular Lineages in Prokaryotes	150
9.4.1	Cell-Membrane Progesterone Receptors	131	11.2.2	Multicellular Lineages in Eukaryotes	150
9.4.2	Cell-Membrane Mineralocorticoid and Glucocorticoid Receptors	131	11.2.2.1	Chromalveolates – Generally Unicellular but with One Multicellular Clade	151
9.4.3	Cell-Membrane Thyroid Hormone and Vitamin A/D Receptors	131	11.2.2.2	Archaeplastida – Algae and Plants	151
9.4.4	Ligand-Independent Activation of Transcription	131	11.2.2.3	Amoebozoans, Fungi, Choanoflagellates, and Animals	151
	<b>Part IV Applications</b>	<b>133</b>	11.3	The Origin of Symmetry and Axes	152
<b>10</b>	<b>Signaling Complexity</b>	<b>135</b>	11.3.1	The Multicellular Body Plan	152
10.1	Introduction	135	11.3.2	The Porifera – Asymmetric with a Single Cell Layer	152
10.2	Experimental Determination of Signaling Cascades	135	11.3.3	Cnidaria – Radial Symmetry, Two Cell Layers, Tissues	153
10.2.1	Glycolysis	135	11.3.4	Mesoderm	154
10.2.2	MAPK: a Phosphorylation Cascade	136	11.4	Fertilization and Organization of the Multicellular Body Plan	154
10.3	Transduction across the Membrane	138	11.4.1	Sperm–Egg Recognition	154
10.3.1	Ion Channels	138	11.4.1.1	Sea Urchin Fertilization	154
10.3.2	G-Protein-Coupled Receptors	138	11.4.1.2	Mammalian Fertilization	157

11.5	Differentiation of Triploblastic Embryos – Organogenesis	158	12.3.1	Pathogenesis of Cancer	177
11.5.1	Introduction	158	12.3.2	Cancer as a Disease of Signaling Molecules	178
11.5.2	The Origin of Triploblastic Animals	158	12.3.2.1	Oncogenes that Encode Mutated Transmitters	178
11.5.3	Development in Protostomes	159	12.3.2.2	Oncogenes that Encode Mutated RTKs	178
11.5.3.1	Segmentation and Organ Formation in <i>Drosophila</i>	159	12.3.2.3	Oncogenes that Encode Mutated G Proteins	179
11.5.3.2	Cellular Interactions in Later <i>Drosophila</i> Development	161	12.3.2.4	Oncogenes that Encode Mutated Transcription Factors – Steroid Receptors	180
11.5.4	Development in Deuterostomes	162			
11.5.4.1	Early Frog Development	162			
11.5.4.2	Nerve Growth	164			
11.6	Programmed Cell Death (Apoptosis)	165	<b>13</b>	<b>Receptors and the Mind</b>	<b>181</b>
11.6.1	Apoptosis During Development	166	13.1	Origins of Behavior	181
11.6.2	Apoptosis During Adult Life	166	13.1.1	Bacterial Short-Term Memory	181
<b>12</b>	<b>Receptor Mechanisms in Disease Processes</b>	<b>169</b>	13.1.2	Animals Without True Neural Organization: The Porifera	182
12.1	Genetic Basis for Receptor Function	169	13.1.3	Animals with Neural Networks: The Cnidaria	182
12.1.1	Genotype and Phenotype	169	13.1.4	Bilaterally Symmetrical Animals: The Acoela	183
12.1.2	Classical Dominance Mechanisms	169	13.2	Nervous Systems	183
12.1.3	Other Levels of Gene Expression	170	13.2.1	Organization	183
12.1.4	Pre-receptor Mutations	170	13.2.2	Neurons	183
12.1.5	Receptor Mutations	171	13.2.2.1	Cell Structure	183
12.1.6	Post-receptor Mutations	171	13.2.2.2	Mechanisms	184
12.2	Receptor Pathologies	171	13.2.3	Transmitters	184
12.2.1	Ion Channel Superfamily	171	13.2.3.1	Synthesis and Release of Brain Transmitters	185
12.2.1.1	Calcium Channels	172	13.2.3.2	Converting Short-Term Memory to Long Term	186
12.2.1.2	Transient Receptor Protein (TRP) Channels	172	13.3	Animal Memory: Invertebrates	186
12.2.1.3	Voltage-Gated Na <sup>+</sup> Channels	172	13.3.1	Discovery of the Signaling Contribution to Memory	186
12.2.1.4	Ligand-Gated Na <sup>+</sup> Channels	172	13.3.2	Receptor Mechanisms of Nerve Cell Interactions	186
12.2.1.5	Chloride Transporter – Cystic Fibrosis	172	13.3.2.1	The Gill Withdrawal Reflex of Aplysia	186
12.2.2	G-Protein-Coupled Receptor Superfamily	172	13.3.2.2	Mechanisms Underlying Sensitization and Short-Term Memory	187
12.2.2.1	Cholera	172	13.3.2.3	Ion Flows in Nerve Action Potentials	187
12.2.2.2	Thyroid Diseases	173	13.3.2.4	Consolidation into Long-Term Memory (LTP)	188
12.2.2.3	Cardiovascular Disease	173	13.4	Animal Memory: Vertebrates	188
12.2.2.4	Obesity	174	13.4.1	Intracellular Mechanisms of Potentiation	188
12.2.2.5	Depression	175	13.5	Receptors and Behavior: Addiction, Tolerance, and Dependence	190
12.2.2.6	Schizophrenia	175	13.5.1	Opioid Receptors	190
12.2.3	Immunoglobulin Superfamily	176	13.5.1.1	Opioid Neuron Pathways in the Brain	191
12.2.3.1	Diabetes Mellitus	176			
12.2.3.2	Atherosclerosis	176			
12.2.4	Nuclear Receptor Superfamily – Steroid Receptors	176			
12.2.4.1	Alterations in Transcription	176			
12.2.4.2	Additional Effects	177			
12.3	Signaling Mutations Leading to Cancer	177			

13.5.1.2	The Opioid Peptides and Receptors	192	14.3.1.2	The Anterior Pituitary Trophic Hormones	203
13.5.1.3	Mechanisms of Transduction	192	14.3.1.3	The Hypothalamic Releasing Hormones	203
13.5.1.4	Characteristics of Responses to Continued Drug Presence	192	14.3.1.4	The Posterior Pituitary Hormones	203
13.5.2	Individual and Cultural Distributions of Depression	193	14.3.1.5	Miscellaneous Peptide Hormones	204
13.5.2.1	Depression	193	14.3.2	Hormones of the Receptor Tyrosine Kinases	204
13.5.2.2	Polymorphisms in Neurotransmitter Transporters	194	14.3.2.1	The Insulin Family	204
13.5.2.3	Polymorphisms in Opioid Receptor Subtypes	194	14.3.2.2	The Neurotrophins	204
13.5.2.4	Polymorphisms in Enzymes for Transmitter Disposition	194	14.3.2.3	The Growth Hormone Family	204
13.5.2.5	Society-Level Actions	194	14.4	Evolution of Receptor Superfamilies	205
13.5.2.6	Possible Mechanisms	195	14.4.1	Ion Channels	205
<b>14</b>	<b>Evolution of Receptors, Transmitters, and Hormones</b>	<b>197</b>	14.4.1.1	Voltage-Gated Channels	205
14.1	Introduction	197	14.4.1.2	Ligand-Gated Channels	205
14.1.1	Phylogeny of Communication: General Ideas	197	14.4.2	G Protein-Coupled Receptors	206
14.1.2	The Receptors	197	14.4.2.1	G-Protein-Coupled Receptor Types	206
14.2	Origins of Transmitters and Receptors	197	14.4.2.2	Family A Receptors – Rhodopsin Family	206
14.2.1	Evolution of Signaling Processes	197	14.4.2.3	Family B – Secretin and Adhesion Receptors	207
14.2.2	Homologous Sequences	198	14.4.2.4	Family F – Frizzled and Smoothened Receptors	208
14.2.2.1	Orthologous and Paralogous Sequences	198	14.4.2.5	Elements of the GPCR Transduction Pathway	208
14.2.3	Phylogenetic Inference	199	14.4.3	The Immunoglobulin Superfamily	210
14.2.4	Phylogenetic Illustration of Protein Relationships	199	14.4.3.1	The Receptor Tyrosine Kinases	210
14.2.5	Whole-Genome Duplication (WGD)	200	14.4.3.2	Molecules of the Adaptive Immune System	211
14.2.6	Origins of Novel Domains	201	14.4.4	Steroid, Vitamin A/D, and Thyroid Hormone Receptors	211
14.2.7	Adaptation of Receptor Systems	201	14.4.4.1	Origin of Nuclear Receptors: The Role of Ligands	211
14.2.8	Coevolution of Components of Signaling Pathways	202	14.4.4.2	The Nuclear Receptor Families	211
14.2.9	Peptide Hormones and Their Receptors	202	14.4.4.3	Later Evolution of Nuclear Receptors – Ligand Exploitation	212
14.2.10	Receptors and Their Non-Peptide Hormones	202	14.5	Evolution of Receptor Antagonism	213
14.3	Evolution of Hormones	202	14.6	A Final Note	213
14.3.1	Peptide Hormones for G Protein-Coupled Receptors	202		<b>Glossary</b>	<b>215</b>
14.3.1.1	The Yeast Mating Pheromones	203		<b>References</b>	<b>227</b>
				<b>Index</b>	<b>241</b>