

Contents

Contributors xi

Preface xv

The Use of GPCR Structures in Drug Design I

Miles Congreve, Christopher Langmead, and Fiona H. Marshall

- I. Introduction 1
- II. Technology Developments Enabling GPCR Structure Determination 2
- III. GPCR Structures 6
- IV. GPCR Structures in Drug Discovery 18
- V. Conclusion 27
- Acknowledgments 29
- References 29

Allosteric Modulation of Metabotropic Glutamate Receptors 37

Douglas J. Sheffler, Karen J. Gregory, Jerri M. Rook, and P. Jeffrey Conn

- I. Introduction 38
- II. Metabotropic Glutamate Receptors 39
- III. Pharmacological Profiles of mGlu Allosteric Modulators 46
- IV. Quantifying Allosteric Interactions 48
- V. Structural Determinants of mGlu Allosteric Modulator Binding 50
- VI. Functional Selectivity of mGlu Allosteric Modulation 53
- VII. Therapeutic Potential of mGlu Allosteric Modulators 54
- VIII. Conclusion 59
- Acknowledgments 60
- References 62

Refining Efficacy: Exploiting Functional Selectivity for Drug Discovery 79

Diane Gesty-Palmer and Louis M. Luttrell

- I. Introduction 80
- II. GPCRs as Conformational Ensembles 81
- III. The Pluridimensional Nature of GPCR Efficacy 83
- IV. Functionally Selective GPCR Agonism 86
- V. Functional Selectivity and Pharmaceutical Development 90
- VI. Functional Selectivity at the Parathyroid Hormone Receptor 91
- VII. Conclusion 97
- Acknowledgments 97
- References 98

Pharmacological Chaperones for Misfolded Gonadotropin-Releasing Hormone Receptors 109

P. Michael Conn and Alfredo Ulloa-Aguirre

- I. Introduction 110
- II. The Endoplasmic Reticulum Quality Control System 111
- III. Misfolding of GPCRs and Disease 115
- IV. Mutations in the Human GnRHR 116
- V. Rescue of Misfolded hGnRHR Mutants with Pharmacoperones 121
- VI. Mechanism of Action of Pharmacoperones 125
- VII. The Dominant-Negative Effect of hGnRHR Mutants and Receptor Rescue 127

VIII. Conclusion	129
Acknowledgments	130
References	131

Regulation of Stability and Trafficking of Calcium-Sensing Receptors by Pharmacologic Chaperones 143

Ying Huang, Alice Cavanaugh, and Gerda E. Breitwieser

I. Introduction	144
II. CaSR: Physiological Contributions to Calcium Homeostasis	144
III. CaSR and Disease	150
IV. Posttranslational Mechanisms Controlling CaSR Abundance	151
V. Pharmacologic Chaperone Contributions to Plasma Membrane Targeting of CaSR	157
VI. Pharmacologic Chaperone Regulation of Organellar CaSR	160
VII. Conclusion	161
Acknowledgments	161
References	162

Experimental Challenges to Targeting Poorly Characterized GPCRs: Uncovering the Therapeutic Potential for Free Fatty Acid Receptors 175

B. D. Hudson, Nicola J. Smith, and Graeme Milligan

I. Introduction	176
II. Deorphanization of the Receptors for FFAs	178
III. Uncovering the Pharmacology of FFA Receptors	182
IV. Synthetic Ligands for FFA Receptors	191
V. Therapeutic Potential for FFA Receptors	200
VI. Conclusion	206
Acknowledgments	207
References	207

Biological and Pharmacological Roles of HCA Receptors 219

Clara C. Blad, Kashan Ahmed, Ad.P. IJzerman, and Stefan Offermanns

I. Introduction	220
II. Identification and Characterization of HCA Receptors	220
III. Gene Structure and Tissue Distribution	224
IV. Physiological and Pharmacological Roles of HCA Receptors	225
V. Receptor Classification with Pharmacological Tools	229

VI. Mutagenesis and Receptor-Modeling Studies	234
VII. Signal Transduction and Receptor Desensitization	236
VIII. Therapeutic Potential of HCA Receptor Ligands	238
IX. Conclusion	241
Acknowledgments	242
References	243

Pharmacology, Signaling and Physiological Relevance of the G Protein-coupled Receptor 55 251

Nariman A. B. Balenga, Christopher M. Henstridge, Julia Kargl, and Maria Waldhoer

I. Introduction	252
II. The G Protein-Coupled Receptor 55	253
III. Biological Relevance of GPR55	263
IV. Conclusion	270
Acknowledgments	271
References	272

Role of PDZ Proteins in Regulating Trafficking, Signaling, and Function of GPCRs: Means, Motif, and Opportunity 279

Guillermo Romero, Mark von Zastrow, and Peter A. Friedman

I. Introduction	280
II. PDZ Proteins	281
III. GPCRs with Carboxy-Terminal PDZ Recognition Motifs	282
IV. PDZ Protein Regulation of GPCR Signaling	302
V. Conclusion	303
Acknowledgments	304
References	305

Regulator of G Protein Signaling Proteins as Drug Targets: Current State and Future Possibilities 315

Benita Sjögren

I. Introduction	316
II. RGS Proteins Regulate Signaling via GPCRs	316
III. Regulation of RGS Protein Function and Expression	322
IV. Noncanonical Functions of RGS Proteins	327
V. Biological Functions of RGS Proteins—Implications in Drug Discovery	329
VI. Advances in RGS Protein Drug Discovery	334

VII. The Future of Targeting RGS Proteins in Drug Discovery	336
VIII. Conclusion	338
References	339

GPCR-Interacting Proteins, Major Players of GPCR Function 349

Pascal Maurice, Jean-Luc Guillaume, Abia Benleulmi-Chaachoua, Avasi M. Daulat, Maud Kamal,
and Ralf Jockers

I. Introduction	349
II. Biosynthesis and Cell Surface Targeting of GPCRs	350
III. Modulation of GPCR Signaling	356
IV. Endocytosis and Recycling of GPCRs	364
V. Conclusion	367
Acknowledgments	369
References	370

Index 381

Recent Volumes in the Serial 391