CONTENTS

Contributors xiii
Preface xvii

1. Evolution of Genes for Incretin Hormones and their Receptors 1
   David M. Irwin
     I. Introduction 2
     II. Evolution on Incretin Hormone Genes 5
     III. Evolution of Incretin Hormone Receptor Genes 12
     IV. Evolution of Incretins 15
     Acknowledgments 16
     References 17

2. Pleiotropic Actions of the Incretin Hormones 21
   Christopher H. S. McIntosh, Scott Widenmaier, and Su-Jin Kim
     I. Introduction 22
     II. GIP and GLP-1 Actions: Hormonal and Neuronal Pathways 24
     III. Effects of GIP and GLP-1 on Early Events During Feeding 27
     IV. Effects of Incretins on Functions of the Endocrine Pancreas 28
     V. Effects of GLP-1 on Food Intake and Satiety 44
     VI. Gastrointestinal Effects of GIP and GLP-1 46
     VII. Cardiovascular Effects of GIP and GLP-1 48
     VIII. Effects of GIP and GLP-1 on Nutrient Storage and Flux 51
     IX. Effects of GIP and GLP-1 on Bone 54
     X. The Future 55
     Acknowledgments 56
     References 56

3. Dietary Effects on Incretin Hormone Secretion 81
   Tongzhi Wu, Christopher K. Rayner, Karen Jones, and Michael Horowitz
     I. Introduction 82
     II. Physiology of the Incretin Hormones 82
     III. Dietary Influence on Incretin Hormone Secretion 85
     IV. Mechanisms by Which Nutrients Stimulate Incretin Release 92
     V. Incretin Responses in Obesity and Diabetes 97
VI. Therapeutic Implications 98
VII. Conclusions 100
Acknowledgments 101
References 101

4. K-cells and Glucose-Dependent Insulinotropic Polypeptide in Health and Disease 111
Young Min Cho and Timothy J. Kieffer

I. History of K-cells and GIP 112
II. The GIP Gene and Regulation of its Expression 115
III. Anatomical Localization and Development of K-cells 117
IV. Secretion, Degradation, and Elimination of GIP 120
V. Biological Actions of GIP 126
VI. GIP and K-cells in Health and Disease 128
VII. Clinical Application of GIP and K-cells 133
References 135

5. The Emerging Role of Promiscuous 7TM Receptors as Chemosensors for Food Intake 151
Petrine Wellendorph, Lars Dan Johansen, and Hans Bräuner-Osborne

I. Introduction 153
II. Family C Receptors as Promiscuous Sensors for l-α-Amino acids, Peptides, Divalent cations, and Carbohydrates 153
III. Family A Receptors as Promiscuous Sensors for Peptone and Free Fatty Acids (FFAs) 164
IV. Therapeutie Perspectives 174
Acknowledgments 175
References 175

6. Central Regulation of Glucose-Dependent Insulinotropic Polypeptide Secretion 185
Maria P. Yavropoulou and John G. Yovos

I. Introduction 186
II. Structure and Action of GIP 186
III. Regulation of GIP Secretion 187
IV. Neural Regulation of GIP Secretion 188
V. The Role of Autonomic Nervous System 188
VI. Concluding Remarks 196
References 196
7. Incretin Hormone Secretion Over the Day
   Bo Ahren, Richard D. Carr, and Carolyn F. Deacon
   I. Introduction 204
   II. GIP and GLP-1 Secretion After Meal Ingestion 204
   III. Regulation of GIP and GLP-1 Secretion 206
   IV. Mechanisms of GIP and GLP-1 Secretion 209
   V. GIP and GLP-1 Secretion Over the Day 209
   VI. Incretin Hormone Secretion in Glucose Intolerance and Disease States 211
   VII. GIP and GLP-1 Secretion in Fasting State 214
   VIII. Conclusion and Perspective 215
   Acknowledgments 216
   References 216

8. Using the Lymph Fistula Rat Model to Study Incretin Secretion
   Stephanie M. Yoder, Tammy L. Kindel, and Patrick Tso
   I. Introduction 222
   II. The Incretin Hormones 223
   III. Anatomy and Physiology of the Gastrointestinal and Lymphatic Systems 227
   IV. The Lymph Fistula Model 229
   V. Using the Lymph Fistula Rat Model to Study Incretin Secretion 232
   VI. Concluding Remarks and Future Directions 242
   Acknowledgments 244
   References 244

9. Structural Basis for Ligand Recognition of Incretin Receptors
   Christina Rye Underwood, Christoph Parthier, and Steffen Reedtz-Runge
   I. G-Protein-Coupled Receptors 252
   II. The GLP-1 Receptor 254
   III. The GIP Receptor 267
   IV. Common and Divergent Features of GLP-1R and GIPR Ligand Binding 271
   References 274

10. Epac2-Dependent Rap1 Activation and the Control of Islet Insulin Secretion by Glucagon-Like Peptide-1
    Colin A. Leech, Oleg G. Chepurny, and George G. Holz
    I. Introduction 280
    II. PKA and Epac2 Regulate Insulin Secretion from β Cells 280
    III. Epac2 Activates Rap1 GTPase 283
    IV. Rap1 Effectors and Their Potential Roles in the Control of GSIS 285
V. Interactions of Epac2 with Secretory Granule-Associated Proteins 294
VI. Conclusions 296
Acknowledgment 297
References 297

11. Central GLP-1 Actions on Energy Metabolism 303
Douglas A. Velásquez, Daniel Beiroa, María J. Vázquez, Amparo Romero,
Miguel López, Carlos Diéguez, and Ruben Nogueiras

I. Introduction 304
II. CNS Glucagon-Like Peptide 1 and Energy Intake 305
III. CNS Glucagon-Like Peptide 1 and Glucose Metabolism 308
IV. CNS Glucagon-Like Peptide 1 and Lipid Metabolism 310
V. Future Directions 311
Acknowledgments 313
References 313

12. Glucagon-Like Peptide-1: Gastrointestinal Regulatory Role in Metabolism and Motility 319
Per M. Hellström

I. Introduction 320
II. GLP-1 in Metabolism 321
III. GLP-1 in Satiety 323
IV. GLP-1 in GI Motility 324
V. GLP-1 in Perspective 327
Acknowledgments 328
References 328

13. The Role of GLP-1 in Neuronal Activity and Neurodegeneration 331
Christian Hölscher

I. A Causal Link Between Diabetes and Alzheimer's Disease 332
II. An Insulin-Supporting Messenger: Glucagon-Like Peptide-1 334
III. GLP-1 Analogues Have Neuroprotective Effects in Mouse Models of AD 342
IV. Many Other Growth Factors Show Neuroprotective Effects 346
Acknowledgment 347
References 347

14. Wnt and Incretin Connections 355
Custodia García-Jiménez

I. What Are Incretins, What They Do, Where, and How 356
II. WNTs: What They Are and What They Do 360
III. WNT/β-catenin Increases the Synthesis of Incretins 364