

# CONTENTS

Preface .....	xi
<b>1. Insulin and IGF-I Receptor Structure and Binding Mechanism .....</b>	<b>1</b>
<i>Pierre De Meyts, Waseem Sajid, Jane Palsgaard, Anne-Mette Jensen, Hassan Aladdin and Jonathan Whittaker</i>	
Evolutionary Biology of the Insulin Peptide Family and Their Receptors .....	1
Structure of the Insulin and IGF-I Receptor Genes and Predicted Protein Tertiary Structure .....	4
Modular Receptor Structures Elucidated by X-Ray Crystallography .....	8
Ligand Binding Properties .....	9
Receptor Crosslinking with Bifunctional and Photoreactive Ligands ...	10
Definition of Ligand Binding Specificity Using Chimeric Insulin/IGF-I Receptors .....	11
Natural Receptor Mutations that Affect Insulin Binding in Syndromes of Extreme Insulin Resistance .....	11
Mapping of Ligand Binding Sites on the Insulin and IGF-I Receptors by Site-Directed and Alanine-Scanning Mutagenesis .....	12
Reconstitution of Modular Minimized Receptor Constructs with Low and High Affinity .....	13
Attempts at Insulin Receptor Structure Definition by Electron Microscopy .....	16
Mapping of Receptor-Binding Sites on the Insulin and IGF-I Molecules .....	17
Mechanism of Ligand Binding and Receptor Activation .....	19
Conclusions and a Word of Caution .....	22
<b>2. Subcellular Compartmentalization of Insulin Signaling Processes and GLUT4 Trafficking Events .....</b>	<b>33</b>
<i>Robert T. Watson, Alan R. Saltiel, Jeffrey E. Pessin and Makoto Kanzaki</i>	
The Insulin Receptor and Its Immediate Downstream Substrate Proteins .....	34
The PI3-Kinase Is Necessary for Insulin-Stimulated GLUT4 Translocation .....	34
Is There a Second Signaling Pathway Required for Insulin-Stimulated Glucose Uptake? .....	37
The APS-CAP-Cbl Pathway Is Compartmentalized Within Plasma Membrane Microdomains .....	38
TC10 Generates Spatially Compartmentalized Signals that Contribute to the Specificity of Insulin Action .....	39
Downstream Targets of TC10 .....	40
Sorting GLUT4 Into and Out of the Insulin-Responsive Storage Compartment .....	43
Does Insulin Regulate the Intrinsic Transport Activity of GLUT4? .....	45
Conclusions and Future Directions .....	46

<b>3. Regulation of Insulin Action and Insulin Secretion by SNARE-Mediated Vesicle Exocytosis</b> .....	52
<i>Debbie C. Thurmond</i>	
Vesicle Exocytosis .....	52
Insulin Action: GLUT4 Vesicle Translocation .....	55
Insulin Exocytosis in Pancreatic Beta Cells .....	58
Perspectives .....	62
<b>4. Control of Protein Synthesis by Insulin</b> .....	71
<i>Joseph F. Christian and John C. Lawrence, Jr.</i>	
mRNA .....	71
Ribosomes .....	74
Initiation .....	75
Elongation .....	80
Termination .....	81
The mTOR Signaling Pathway .....	81
<b>5. Hepatic Regulation of Fuel Metabolism</b> .....	90
<i>Catherine Clark and Christopher B. Newgard</i>	
Glucose Transport .....	90
Glycolysis .....	91
Gluconeogenesis .....	97
Glycogen Metabolism .....	101
New Developments .....	104
<b>6. Insulin Action Gene Regulation</b> .....	110
<i>Calum D. Sutherland, Richard M. O'Brien and Daryl K. Granner</i>	
Insulin Signal Transduction and Gene Expression .....	113
Key Insulin-Regulated Gene Promoters .....	120
Coordinated Regulation of PEPCK, G6Pase, IGFBP-1 and TAT Gene Expression? .....	123
<b>7. Insulin Action in the Islet <math>\beta</math>-Cell</b> .....	133
<i>Rohit N. Kulkarni</i>	
Embryonic and Early Post-Natal Development of the Endocrine Pancreas .....	135
Global and Conditional Knockouts of Insulin, IGF-I, IGF-II, and Proteins in Their Signaling Pathways .....	137
Maintenance of Adult $\beta$ -Cell Mass .....	140
Growth and Development of Islet $\alpha$ -Cells .....	143
The Liver-Pancreas Connection .....	144
Future Insights .....	145

<b>8. Central Regulation of Insulin Sensitivity</b> .....	152
<i>Silvana Obici and Luciano Rossetti</i>	
Insulin Action in the Hypothalamus .....	154
Central Effects of Leptin on Insulin Sensitivity .....	158
Hypothalamic Lipid Sensing .....	161
<b>9. Transgenic Models of Impaired Insulin Signaling</b> .....	168
<i>Francesco Oriente and Domenico Accili</i>	
Insulin Receptor Knockout .....	168
Conditional <i>Insulin Receptor</i> Knockouts .....	169
Mutations Affecting Insulin Receptor Signaling .....	173
Gene Knockouts Associated with Increased Insulin Sensitivity .....	177
<b>10. Insulin Resistance</b> .....	185
<i>C. Hamish Courtney and Jerrold M. Olefsky</i>	
Methods of Assessing Insulin Sensitivity .....	185
Insulin Resistance in Type 2 Diabetes Mellitus and Obesity .....	187
<b>Index</b> .....	211