

Contents

Preface *XIII*

A Personal Foreword *XVII*

1 Insights into Transporter Classifications: an Outline of Transporters as Drug Targets *1*

Michael Viereck, Anna Gaulton, and Daniela Digles

- 1.1 Introduction *1*
- 1.2 Available Transporter Classifications *2*
 - 1.2.1 TCDB *2*
 - 1.2.2 IUPHAR/BPS *5*
 - 1.2.3 ChEMBL-16 and ChEMBL-18 *5*
 - 1.2.4 SLC Series *6*
- 1.3 Function versus Sequence Similarity *7*
- 1.4 Merged Top-Level Transporter Classification *7*
- 1.5 Choice and Design of the New ChEMBL Classification *11*
- 1.6 Transporter as Drug Targets *12*
- 1.7 Drug Targets in the SLC Classification *15*
- 1.8 Conclusions *17*
 - Acknowledgment *17*
 - References *18*

2 New Trends in Antidepressant Drug Research *21*

Benny Bang-Andersen, Klaus P. Bøgesø, Jan Kehler, and Connie Sánchez

- 2.1 Introduction *21*
 - 2.1.1 Major Depressive Disorder and Antidepressant Drugs *21*
 - 2.1.2 Antidepressant Drug Nomenclature *22*
 - 2.1.3 Disease Biology of Depression and Antidepressant Drugs *24*
 - 2.1.4 Single-Target versus Multitarget Compounds, Including Combination Therapy *25*
- 2.2 Reuptake Blockers *26*
 - 2.2.1 Single-Target Drugs *26*
 - 2.2.1.1 Selective Serotonin Reuptake Inhibitor and Allosteric Serotonin Reuptake Inhibitor *26*

- 2.2.1.2 Selective Allosteric Serotonin Transporter Modulator 27
- 2.2.1.3 Selective Norepinephrine Reuptake Inhibitor 30
- 2.2.2 Multitarget Drugs 32
 - 2.2.2.1 Serotonin and Norepinephrine Reuptake Inhibitors 32
 - 2.2.2.2 Serotonin, Norepinephrine, and Dopamine Reuptake Inhibitors (SNDRIs or Triple-uptake Inhibitors) 33
 - 2.2.2.3 Other Combinations of Monoamine Transporter Inhibitors 36
- 2.3 Multimodal Drugs 36
 - 2.3.1 Toward Multimodal Antidepressants, Exemplified by the Combined SERT Inhibitors and 5-HT_{1A} Receptor Antagonists 37
 - 2.3.2 Vilazodone 37
 - 2.3.3 Vortioxetine 38
- 2.4 Conclusions 42
 - List of Abbreviations 42
 - References 43

3 The Molecular Basis of the Interaction Between Drugs and Neurotransmitter Transporters 53

Harald H. Sitte, Thomas Stockner, and Michael Freissmuth

- 3.1 Introduction 53
- 3.2 Crystal Structures of SLC6 Transporters 55
- 3.3 The Binding Site Proper 60
- 3.4 The Transport Cycle 61
- 3.5 Conclusions and Perspectives 63
 - Acknowledgments 64
 - References 64

4 γ -Aminobutyric Acid and Glycine Neurotransmitter Transporters 69

Petrine Wellendorph, Julie Jacobsen, Jonas Skovgaard-Petersen, Andreas Jurik, Stine B. Vogensen, Gerhard Ecker, Arne Schousboe, Povl Krosgaard-Larsen, and Rasmus P. Clausen

- 4.1 Introduction 69
 - 4.1.1 Inhibitory Neurotransmission at GABAergic and Glycinergic Synapses 70
 - 4.1.1.1 Transporter-Mediated Substrate Transport 70
 - 4.1.1.2 General Topological and Structural Features 72
 - 4.1.2 GAT and GLYT Subtypes 72
- 4.2 GABA Transporters 73
 - 4.2.1 Localization of GATs 73
 - 4.2.2 Molecular Pharmacology of GATs 73
 - 4.2.2.1 Transporter Structure–Function Studies 76
 - 4.2.2.2 Medicinal Chemistry: GABA Uptake Inhibitors 78
 - 4.2.2.2.1 Small Substrate-Related Analogs and Early Development 78
 - 4.2.2.2.2 Prodrug Design and Lipophilic GAT Inhibitors with Increased BBB Penetration 80

4.2.3.3	Recent Development of Inhibitors	82
4.2.4	Therapeutic Potential of GAT Inhibitors	85
4.2.4.1	Role in Epilepsy/Anticonvulsive Therapy	85
4.2.4.2	Animal Models of Anticonvulsant Action	86
4.2.4.3	GAT Inhibitors and Epilepsy	87
4.2.4.4	New Emerging Area: Therapeutic Potential of GATs in the Recovery of Stroke	89
4.3	Glycine Transporters	90
4.3.1	Localization of GLYT _s	90
4.3.2	GLYT Physiology	90
4.3.2.1	Function of GLYT ₁ at Excitatory Synapses	90
4.3.2.2	Lessons from GLYT Knockout Mice	91
4.3.3	Molecular Pharmacology of GLYT _s	91
4.3.4	GLYT Inhibitors	92
4.3.4.1	GLYT ₁ Inhibitors	92
4.3.4.2	GLYT ₂ Inhibitors	93
4.3.5	Therapeutic Potential of GLYT Inhibitors	94
4.4	Conclusions and Future Perspectives	95
	References	96
5	ABC Transporters: From Targets to Antitargets and Back	107
	<i>Gerhard F. Ecker</i>	
5.1	Introduction	107
5.2	ABC Transporter as Drug Targets	109
5.3	ABC Transporter: from Targets to Antitargets	111
5.4	Pharmacochaperones and Beyond	113
5.5	Conclusions and Outlook	114
	Acknowledgment	115
	References	115
6	ABC Transporters Involved in Cholestasis	119
	<i>Frans J. C. Cuperus, Julien Gautherot, Emina Halilbasic, Thierry Claudel, and Michael Trauner</i>	
6.1	Introduction	119
6.2	Canalicular ABC Transporters	122
6.2.1	ABCB ₁₁	122
6.2.2	ABCC ₂	126
6.2.3	ABCB ₁	128
6.2.4	ABCB ₄	131
6.2.5	ABCG ₂	133
6.2.6	ABCG _{5/8}	135
6.3	Basolateral ABC Transporters	136
6.3.1	ABCC ₃	136
6.3.2	ABCC ₄	138
6.4	Nuclear Receptors as Drug Targets	140

6.5	Ursodeoxycholic Acid Treatment in Cholestatic Liver Disease	144
6.6	Conclusions	145
	References	145
7	Recent Advances in Structural Modeling of ABC Transporters	167
	<i>Dennis Haake, Peter Chiba, and Gerhard F. Ecker</i>	
7.1	Introduction	167
7.2	ABC Transporter Modeling Attempts Since 2001	168
7.3	Retraction of Five Transporter Structures	170
7.4	First Mammalian ABC Transporter Structure	173
7.5	Conclusions and Perspectives	175
	Acknowledgment	175
	References	175
8	PET Imaging of ABC Transporters at the Blood–Brain Barrier	179
	<i>Oliver Langer</i>	
8.1	The Blood–Brain Barrier	179
8.2	The Brain as a Pharmacological Sanctuary	180
8.3	Implication of ABC Transporters in Neurological Disorders	180
8.4	Positron Emission Tomography	181
8.5	PET Imaging of ABC Transporters	181
8.6	Challenges in Designing PET Tracers for ABC Transporters	184
8.7	Potential Applications of PET Tracers for ABC Transporters	184
8.8	Overview of Available PET Tracers for Cerebral ABC Transporters	185
8.8.1	Radiolabelled P-gp Substrates	185
8.8.1.1	Racemic [¹¹ C]verapamil and (R)-[¹¹ C]verapamil	185
8.8.1.2	[¹¹ C]Loperamide and [¹¹ C]-N-Desmethyl-Loperamide	186
8.8.2	Radiolabelled P-gp Inhibitors	187
8.8.2.1	¹¹ C- and ¹⁸ F-Labeled Tariquidar	187
8.8.2.2	¹¹ C- and ¹⁸ F-Labeled Elacridar	188
8.8.2.3	[¹¹ C]Laniquidar	189
8.8.3	Radiolabelled BCRP Substrates	189
8.8.3.1	[¹¹ C]Dantrolene	189
8.8.4	Radiolabelled Dual P-gp/BCRP Substrates	189
8.8.5	Radiolabelled MRP1 Substrates	190
8.9	Summary	191
	Abbreviations	191
	References	191
9	The Systems Biology of Transporters – Targeting the Regulatory System for Transporters (FXR/RXR)	199
	<i>Antimo Gioiello, Maura Marinozzi, Bruno Cerra, Chiara Custodi, Roberto Pellicciari, and Antonio Macchiarulo</i>	
9.1	Introduction	199
9.2	Discovery and Pharmacological Characterization of FXR	200

9.3	Regulation of the Hepatobiliary Transport System by FXR	201
9.3.1	Direct Mechanisms	202
9.3.2	Indirect Mechanisms	205
9.4	Genetic and Structural Properties of FXR	207
9.5	FXR Ligands	209
9.5.1	Natural Compounds and Derivatives	209
9.5.1.1	Bile Acids and Derivatives	209
9.5.1.2	Guggulsterones	211
9.5.1.3	Triterpenes	212
9.5.1.4	Sterols and Polyhydroxylated Sterol Derivatives	213
9.5.1.5	Miscellaneous Natural Compounds and Derivatives	214
9.5.2	Nonsteroidal Compounds	215
9.5.2.1	GW4064 and Derivatives	215
9.5.2.2	Fexaramine and Derivatives	217
9.5.2.3	FXR450 and Derivatives	217
9.5.2.4	Benzimidazole Derivatives and Retinoic Acid-Related Compounds	218
9.5.2.5	Virtual Screening Campaigns	219
9.6	Conclusions and Perspectives	221
	References	221
10	ANO1 as a Novel Drug Target	231
	<i>Anke Bill and Larry Alex Gaither</i>	
10.1	Introduction	231
10.2	ANO1: a Calcium Activated Chloride Channel	232
10.2.1	The Discovery of ANO1	232
10.2.2	Anoctamins	233
10.2.3	Structure of ANO1	234
10.2.4	Biophysical Properties of ANO1	234
10.2.5	Expression and Physiological Role of ANO1	235
10.2.6	ANO1 and Cancer	236
10.3	Pharmacological Targeting of ANO1	238
10.3.1	Small-Molecule Inhibitors of ANO1	238
10.3.2	Activators of ANO1	240
10.3.3	Natural Products	240
10.4	ANO1 as a Therapeutic Target	241
10.4.1	Cystic Fibrosis	241
10.4.2	Asthma	242
10.4.3	Diarrhea	242
10.4.4	Cancer	243
10.4.5	Others	245
10.4.6	Potential Risks of Therapeutic Intervention of ANO1 Activity	245
10.5	Concluding Remarks	246
	References	247

11	Ligand Discovery for the Nutrient Transporters ASCT2 and LAT-1 from Homology Modeling and Virtual Screening	253
	<i>Claire Colas and Avner Schlessinger</i>	
11.1	Solute Carriers in Cancer Metabolism	253
11.2	<i>In Silico</i> Methods for Structure-based Drug Design	255
11.2.1	Homology Modeling	256
11.2.2	Transporter Dynamics	259
11.2.3	Ligand Prediction	259
11.3	Emerging Cancer Metabolism Targets	260
11.3.1	ASCT2	260
11.3.2	LAT-1	262
11.4	Conclusions and Future Outlook	263
	Acknowledgment	265
	References	265
12	Organic Anion Transporting Polypeptides as Drug Targets	271
	<i>Eleni Kotsampasakou and Gerhard F. Ecker</i>	
12.1	Introduction	271
12.1.1	Family OATP1	279
12.1.2	Subfamily OATP1A	279
12.1.3	Subfamily OATP1B	279
12.1.4	Subfamily OATP1C	280
12.1.5	Family OATP2	281
12.1.6	Subfamily OATP2A	281
12.1.7	Subfamily OATP2B	282
12.1.8	Family OATP3	282
12.1.9	Subfamily OATP3A	282
12.1.10	Family OATP4	283
12.1.11	Subfamily OATP4A	283
12.1.12	Subfamily OATP4C	284
12.1.13	Family OATP5	284
12.1.14	Subfamily OATP5A	284
12.1.15	Family OATP6	284
12.1.16	Subfamily OATP6A	285
12.2	OATPs and Genetic Diseases	285
12.3	OATPs and Cancer	286
12.3.1	Breast Cancer	293
12.3.2	Ovarian Cancer	294
12.3.3	Prostate Cancer	295
12.3.4	Colorectal Cancer	297
12.3.5	Liver Cancer	298
12.3.6	Pancreatic Cancer	299
12.3.7	Small-Cell Lung Cancer	299
12.3.8	OATPs and Other Forms of Cancer	300
12.4	OATPs as Diagnostic Markers	301

12.5	OATPs and Selective Delivery of Drugs	301
12.5.1	OATPs and Intestinal Drug Absorption	302
12.5.2	OATPs and Targeted Liver Drug Delivery	303
12.5.3	Statins	304
12.5.4	Glucokinase Activators	306
12.5.5	Stearoyl-CoA Desaturase-1 Inhibitors	307
12.5.6	OATPs and Targeted Pancreas Drug Delivery	307
12.5.7	OATPs and CNS Drug Delivery	308
12.6	Potential Protective Role of OATPs	309
12.6.1	OATP4C1 versus Chronic Kidney Disease	309
12.6.2	OATPs versus Amatoxins	310
12.7	OATPs and Drug–Drug Interactions	311
12.8	Conclusions and Outlook	312
	Acknowledgments	313
	Abbreviation List	313
	References	314
	Index	325

