

Contents

1	Introduction to Compartmental Analysis	1
1.1	Concept of Compartments	1
1.1.1	Living Systems	1
1.1.2	Thermodynamics and Entropy	3
1.1.3	Fundamental Solution	6
1.1.4	Limitations of Compartmental Analysis	6
1.2	Single Tissue Compartment Analysis	7
1.3	Two Tissue Compartment Analysis	9
1.3.1	Compartmental Assumptions	9
1.3.2	Combined Compartments	12
1.3.3	Arteries and Veins	13
1.4	Three Tissue Compartment Analysis	14
1.4.1	Compartmental Assumptions	15
1.4.2	Combined Compartments	20
2	Fundamentals of Compartmental Kinetics	23
2.1	Definition of Relaxation Constants	23
2.1.1	Single Compartment	24
2.1.2	Two Compartments	25
2.1.3	Two Compartments with Sink	28
2.1.4	Three Compartments	30
2.1.5	Three Compartments with Sink	34
2.1.6	Four or More Compartments	36
2.1.7	Multiple Compartments in Series and in Parallel	39
2.2	Interpretation of Relaxation Constants	42
2.2.1	Flow	42
2.2.2	Passive Diffusion	43
2.2.3	Properties of Delivery Compartment	49
2.2.4	Protein–Ligand Interaction	56
2.2.5	Receptor Binding	61

2.2.6	Facilitated Diffusion	63
2.2.7	Enzymatic Reactions	67
2.3	Determination of Relaxation Constants	70
2.3.1	Stimulus-Response Relations	70
2.3.2	Regression Analysis	71
2.3.3	Deconvolution of Response Function by Differentiation	73
2.3.4	Deconvolution by Temporal Transformation	75
2.3.5	Deconvolution of Response Function by Linearization	86
2.4	Application of Relaxation Constants	91
2.4.1	Peroxidation	91
2.4.2	Dopaminergic Neurotransmission	91
3	Analysis of Neuroreceptor Binding In Vivo	103
3.1	The Receptor Concept	103
3.2	The Compartment Concept	105
3.2.1	Compartmental Analysis	105
3.2.2	The Basic Equation	106
3.2.3	The Basic Solution	107
3.3	Two-Compartment (Permeability) Analysis	108
3.3.1	Analysis of K_1 and k_2	108
3.3.2	Physiological Definitions of K_1 and k_2	110
3.4	Three-Compartment (Binding) Analysis	111
3.4.1	Analysis of k_3 and k_4	111
3.4.2	Molecular Definitions of k_3 and k_4	115
3.4.3	Inhibition	118
3.4.4	The Problem of Solubility and Nonspecific Binding	120
3.4.5	The Problem of Labeled Metabolites	122
3.5	In Vivo Analysis of Binding	122
3.5.1	Irreversible Binding: Determination of k_3	122
3.5.2	Reversible Binding: Determination of Binding Potential (p_B)	124
3.5.3	Equilibrium Analysis: Determination of B_{\max} and K_D	126
4	Neuroreceptor Mapping In Vivo: Monoamines	131
4.1	Introduction	131
4.2	Monoaminergic Neurotransmission	131
4.3	Methods of Neuroreceptor Mapping	133
4.3.1	Tracers of Monoaminergic Neurotransmission	136
4.3.2	Pharmacokinetics of Monoaminergic Neurotransmission	140
4.4	Altered Monoaminergic Neurotransmission	145
4.4.1	Dopamine	146
4.4.2	Serotonin	149
4.4.3	Design of Monoaminergic Drugs	151
4.5	Conclusions	151

5	Blood–Brain Transfer and Metabolism of Oxygen	153
5.1	Introduction	153
5.2	Blood–Brain Transfer of Oxygen	154
5.2.1	Capillary Model of Oxygen Transfer	154
5.2.2	Compartment Model of Oxygen Transfer	157
5.3	Oxygen in Brain Tissue	159
5.3.1	Cytochrome Oxidation	159
5.3.2	Mitochondrial Oxygen Tension	161
5.4	Flow–Metabolism Coupling of Oxygen	165
5.5	Limits to Oxygen Supply	167
5.5.1	Distributed Model of Insufficient Oxygen Delivery	168
5.5.2	Compartment Model of Insufficient Oxygen Delivery	171
5.6	Experimental Results	172
5.6.1	Brain Tissue and Mitochondrial Oxygen Tensions	172
5.6.2	Flow–Metabolism Coupling	173
5.6.3	Ischemic Limits of Oxygen Diffusibility	176
6	Blood–Brain Glucose Transfer	177
6.1	Brief History	177
6.2	Brain Endothelial Glucose Transporter	178
6.2.1	Molecular Biology	178
6.2.2	Molecular Kinetics	180
6.2.3	Structural Requirements of Glucose Transport	181
6.3	Theory of Blood–Brain Glucose Transfer	182
6.3.1	Apparent Permeability and Flux	183
6.3.2	Facilitated Diffusion	186
6.3.3	Multiple Membranes	189
6.4	Evidence of Blood–Brain Glucose Transfer	191
6.4.1	Methods	192
6.4.2	Normal Values in Awake Subjects	196
6.4.3	Acute Changes of Glucose Transport	201
6.4.4	Chronic Changes	206
7	Metabolism of Glucose	211
7.1	Basic Principles of Metabolism	211
7.1.1	Glycolysis	212
7.1.2	Oxidative Phosphorylation	214
7.1.3	Gluconeogenesis	214
7.1.4	Glycogenesis and Glycogenolysis	215
7.1.5	Pentose-Phosphate Pathway	215
7.2	Kinetics of Steady-State Glucose Metabolism	215
7.3	Kinetics of Deoxyglucose Metabolism	217
7.3.1	Irreversible Metabolism	219
7.3.2	Lumped Constant	220
7.3.3	Reversible Metabolism	221

7.4	Operational Equations	224
7.4.1	Irreversible Metabolism of Deoxyglucose	224
7.4.2	Reversible Metabolism of Fluorodeoxyglucose	229
7.4.3	Metabolism of Tracer Glucose	231
7.5	Glucose Metabolic Rates	233
7.5.1	Lumped Constant Variability	235
7.5.2	Whole-Brain Glucose Consumption	237
7.5.3	Regional Brain Glucose Consumption	238
8	Neuroenergetics	241
8.1	Brain Work	241
8.2	Ion Homeostasis	242
8.3	Brain Energy Metabolism	244
8.3.1	Definition of Brain Activity Levels	244
8.3.2	Stages of Brain Metabolic Activity	246
8.4	Substrate Transport in Brain	248
8.4.1	Glucose Transport	248
8.4.2	Monocarboxylate Transport	249
8.4.3	Oxygen Transport	250
8.5	ATP Homeostasis	252
8.5.1	Hydrolysis of Phosphocreatine	253
8.5.2	Glycolysis	253
8.5.3	Oxidative Phosphorylation	256
8.6	Metabolic Compartmentation	259
8.6.1	Functional Properties of Neurons and Astrocytes	259
8.6.2	Metabolic Properties of Neurons and Astrocytes	260
8.7	Activation	265
8.7.1	Ion Homeostasis During Activation	266
8.7.2	Brain Energy Metabolism During Activation	267
8.7.3	Substrate Delivery During Activation	273
8.7.4	ATP Homeostasis During Activation	281
8.7.5	Metabolic Compartmentation During Activation	286
8.8	Conclusions	288
	Glossary	291
	References	301
	Index	335

Neurokinetics

The Dynamics of Neurobiology in Vivo

Gjedde, A.; Bauer, W.R.; Wong, D.

2011, XVI, 343 p., Hardcover

ISBN: 978-1-4419-7408-2