
Contents

Preface.....	xv
Acknowledgments.....	xvii
Author	xix

Chapter 1 Nutrition and the Host Response to Infection and Injury	1
1.1 Nutrition and Illness	1
1.1.1 Introduction	1
1.1.2 Infection and Undernutrition.....	2
1.1.3 Nutritional Status and Immune Function.....	2
1.1.4 The Undernutrition-Infection Paradigm.....	2
1.2 Host Response to Injury	3
1.2.1 The Ebb and Flow Phases	3
1.2.2 Molecular Aspects of the Host Response to Injury.....	3
1.2.3 The Infection-Inflammatory Response	5
1.2.4 Neuroendocrine Responses to Illness and Stress.....	5
1.3 Unintended Weight Loss	6
1.3.1 Sickness-Related Weight Loss	6
1.3.2 Illness Anorexia	7
1.3.3 Cachexia	8
1.3.4 Starvation Weight Loss versus Cachexia	10
1.3.5 Fat-Free Mass and Body Composition during Illness.....	11
1.3.6 Weight Loss and Mortality Risk	12
1.3.7 Premature or Preterm Infants.....	12
1.4 Multimodal Nutritional Support Using Bioactive Peptides....	13
1.4.1 Nutritional Support.....	13
1.4.2 Anti-Inflammatory Therapy and Wasting	13
1.4.3 Infection and Antisepsis.....	13
1.4.4 Anabolic Dysfunction	14
1.4.5 Anorexia and Food Intake.....	14
1.4.6 Antioxidant Capacity.....	14
1.5 Summary and Conclusions.....	14
References	16

Chapter 2	Bioactive Peptides for Nutrition and Health.....	21
2.1	Legislation	21
2.1.1	Introduction	21
2.1.2	Dietary Supplements	22
2.1.3	Foods for Special Medical Purposes.....	23
2.1.4	Medical Foods.....	24
2.1.5	EU Legislation for Dietetic Foods.....	26
2.1.6	Functional Foods	27
2.1.7	Protein and Peptide Medical Foods	29
2.2	Bioactive Peptides and Proteins	30
2.2.1	Bioactive Compounds.....	30
2.2.2	Bioactive Peptide–Related Nutritional Phenomena	31
2.2.2.1	Bioactive Peptides in Body Compartments.....	32
2.2.2.2	Exogenous Bioactive Peptides Associated with Foods.....	32
2.2.3	Gene-Encoded Bioactive Peptides	32
2.2.4	Bioactive Peptides and the Cryptome	33
2.2.5	Commercial Bioactive Peptides	34
2.2.6	Nutrigenomics Considerations	34
2.3	Applications of Protein Supplements for Health.....	35
2.3.1	Heterogeneous versus Enriched Supplements.....	35
2.3.2	Bone and Hip Fractures.....	36
2.3.3	Elderly Malnourished Patients	36
2.3.4	Pregnancy	37
2.3.5	Muscle Strength from Resistance Exercise	37
2.3.6	Insulin-Stimulating Activity	37
2.3.7	Protein Supplementation and Cardiovascular Health	38
2.4	Perspectives on Human Trial Data	39
2.4.1	Statistical Effects.....	39
2.4.2	Health Claims for Foods and Supplements.....	40
2.4.3	Safety and Side Effects of Bioactive Peptides and Proteins.....	41
2.5	Summary and Conclusions.....	41
	Appendices	42
	References	48

Chapter 3	Dietary Protein Requirements for Health	59
3.1	Introduction	59
3.1.1	Protein-Energy Undernutrition.....	59
3.1.2	Detection of Protein-Energy Undernutrition.....	60
3.1.3	Incidence and Consequences of Undernutrition	61
3.2	Dietary Protein Quality Relation to Health.....	62
3.2.1	Protein Quality and Nutritive Properties	62
3.2.2	Growth Assays for Dietary Protein Quality.....	63
3.2.3	Nitrogen Balance and Protein Quality	64
3.2.4	Dietary Protein Digestibility Relation to Nitrogen Balance.....	65
3.2.5	Ileal Digestibility and Net Postprandial Protein Utilization.....	66
3.2.6	Dietary and Body Protein Balances and Transformations.....	67
3.3	Protein Requirements and Health.....	68
3.3.1	Adults	68
3.3.2	Protein Requirements for Aging Adults (Elderly)....	69
3.3.3	Protein Requirements for Exercise.....	70
3.3.4	Preterm Infants and Children.....	70
3.4	Dietary Protein and Host Responses to Illness	71
3.4.1	Urea-Nitrogen Losses during Illness.....	71
3.4.2	Acute Phase Protein Synthesis	72
3.4.3	Protein EAA Imbalances during Illness	73
3.5	Peptides and Protein Bioactivity	75
3.5.1	Essential Amino Acid and Dietary Protein Meta-Nutrients	75
3.5.2	Leucine and the Branched Chain Amino Acids	77
3.5.3	Nutrient Signaling and Gene Interactions.....	78
3.5.4	Receptor Activation by Bioactive Peptides	79
3.5.5	Amino Acid Deprivation and Growth Retardation	79
3.5.6	Increased EAA Availability and Gene Expression	82
3.5.7	Microarray Profiling of Dietary Protein–Gene Interactions	82
3.6	Types of Dietary Protein Health Effects	84
3.6.1	Types of Health Benefits	84
3.6.2	Health Benefits and Non-Absorbed Proteins	84
3.7	Summary and Conclusion	85
	Appendices	85
	References	86

Chapter 4	Protein Turnover and Economics within the Body	97
4.1	Protein Turnover and Wasting.....	97
4.1.1	Introduction	97
4.1.2	Biological Purpose of Protein Turnover.....	97
4.1.3	Stable Isotope End Product and Precursor Flux	98
4.1.4	Non-Tracer Methods for Estimation of Turnover.....	100
4.1.5	Protein Turnover Implications for Nutritional Support	101
4.2	Baseline Whole Body Protein Turnover.....	102
4.2.1	Adults	102
4.2.2	Gender and Pregnancy	102
4.3	Regional Protein Turnover.....	103
4.3.1	Splanchnic Bed Protein Kinetics	103
4.3.2	First-Pass Metabolism of Dietary EAA and Interorgan Effects.....	104
4.4	Protein Turnover during Illness.....	105
4.4.1	Preterm Babies and Children	105
4.4.2	Aging Adults and Sarcopenia.....	106
4.4.3	HIV/AIDS Infection	107
4.4.4	Burns Patients.....	108
4.4.5	Cancer Cachexia.....	108
4.4.6	Chronic Renal Failure and Hemodialysis	110
4.4.7	Diabetes.....	110
4.4.8	Sepsis.....	112
4.4.9	Tuberculosis.....	112
4.4.10	Anabolic Dysfunction Affecting Protein Turnover	113
4.5	Nutrients and Protein Turnover	114
4.5.1	Dietary Protein Intake and Whole Body Protein Turnover	114
4.5.2	Skeletal Muscle Protein Turnover	116
4.5.2.1	Animal Studies	116
4.5.2.2	Effect of Nutrients on Skeletal Muscle Protein Turnover—Human Studies	118
4.6	Slow and Fast Proteins	119
4.6.1	Digestion and Absorption Kinetics	119
4.6.2	Effect of Fast Dietary Proteins on Protein Turnover	120
4.6.3	Intrinsic versus Extrinsic Contributions to Fast and Slow Proteins	122
4.6.4	Fast versus Slow Proteins for the Elderly and Young	123
4.6.5	Insulinotropic Action of Fast Proteins	123
4.7	Summary and Conclusions.....	124
	References	124

Chapter 5	Major Processes for Muscle Gain and Loss	135
5.1	Introduction	135
5.1.1	Muscle Cells	135
5.1.2	Muscle Stem Cell Proliferation	137
5.1.3	Muscle Stem Cell Differentiation.....	139
5.1.4	Nutrient Effects on Muscle Stem Cell Growth	140
5.2	Myostatin	140
5.2.1	Double Muscling and Myostatin Mutations	140
5.2.2	Myostatin Structure and Activity	141
5.2.3	Mode of Action of Myostatin	141
5.2.4	Myostatin Role in Wasting Diseases	142
5.2.5	Myostatin Inhibition as Therapy for Muscle Wasting	144
5.3	Muscle Cell Death and Atrophy	144
5.3.1	Types of Cell Death.....	144
5.3.2	Muscle Apoptosis and Necrosis	144
5.3.3	Skeletal Muscle Wasting via Apoptosis	146
5.3.4	Lysosome-Mediated Autophagy	147
5.4	Proteolysis via Ubiquitin Proteasome	149
5.4.1	Enzyme Systems for Muscle Wasting	149
5.4.2	Structure of the Ubiquitin-Proteasome	149
5.4.3	Ubiquitin Proteasome and Muscle Wasting	151
5.4.4	Cell Cycle Regulation and the Proteasome	151
5.4.5	UPS and the Immune Response	153
5.5	Further Signaling Pathways for Muscle Atrophy	153
5.5.1	Skeletal Muscle Differentiation Program.....	154
5.5.2	Nuclear Factor Kappa Beta and Muscle Wasting....	154
5.5.3	MuRF and Atrogin-1 Gene Expression.....	154
5.5.4	AKT/Foxo/Atrogin-1 Pathway and Proteolysis	155
5.5.5	Oxidative Stress and Muscle Wasting	158
5.5.6	Angiotensin-Related Muscle Wasting	158
5.6	Mammalian Target of Rapamycin and Hypertrophy	159
5.6.1	mTOR Function as a Nutrient Sensor	160
5.6.2	Two mTOR Complexes and Their Function.....	160
5.6.3	Regulation of Protein Synthesis by mTOR	162
5.7	Summary and Conclusions.....	162
	Appendices	162
	References	164

Chapter 6	Inflammation and Innate Immune Response	181
6.1	Types of Inflammation	181
6.1.1	Introduction	181
6.1.2	Acute and Chronic Inflammation.....	181
6.1.3	Infection Inflammation.....	184
6.1.4	Obesity-Related Inflammation	185
6.1.5	Chronic Inflammation, Illness, and Lifestyle Factors	187
6.2	Proinflammatory Signaling	188
6.2.1	Proinflammatory Cytokines.....	188
6.2.2	Transcription Factors for Inflammatory Signaling.....	189
6.2.3	Redox-Sensitive Inflammatory Transcription Factors	193
6.2.4	MAP Kinases, Phosphatases, and Inflammation	194
6.2.5	Renin–Angiotensin System and Inflammation	195
6.3	Anti-Inflammatory Bioactive Peptides and Supplements.....	197
6.3.1	Adiponectin	197
6.3.2	Angiotensin-Converting Enzyme Inhibitor Peptides	198
6.3.3	Antimicrobial Peptide Endotoxin Antagonists	199
6.3.4	Cytokine Antibodies	200
6.3.5	Ghrelin and Growth Hormone Secretagogues	200
6.3.6	Glucocorticoid-Inducible Peptides	202
6.3.6.1	Lipocortin or Annexin-1	203
6.3.6.2	Uteroglobin or Clara Cell 10 Protein.....	204
6.3.6.3	Antiflammins.....	205
6.3.7	Map Kinase Inhibitors.....	205
6.3.8	Melanocortin Peptides and KPV	206
6.3.9	Glutamine and Glutamine Dipeptide	209
6.3.10	Food Proteins and Supplements	210
6.4	In Vivo Applications and Controlled Trials	211
6.4.1	Proof for Anti-Inflammatory Action.....	211
6.4.2	Inflammatory Bowel Disease, Colitis, and Mucosal Injury	212
6.4.3	Systemic Inflammatory Response and Sepsis.....	214
6.4.4	Respiratory Distress Syndrome, Lung Injury and Related	215
6.4.5	Rheumatoid Arthritis	217
6.5	Summary and Conclusions	218
	References	219

Chapter 7	Infection and Sepsis	239
7.1	Introduction	239
7.1.1	Bacterial Infections, Sepsis, and Weight Loss	239
7.1.2	Host Antimicrobial Peptides for Innate Defense	240
7.1.3	Antibiotics and Muscle Mass	241
7.2	Pathogen Recognition and Intracellular Signaling.....	242
7.2.1	Toll-Like Receptors.....	242
7.2.1.1	TLR in Peripheral Tissues and Muscles...	243
7.2.1.2	Lipopopolysaccharide Signaling via TLR4.....	245
7.2.1.3	Peptidoglycan Signaling via TLR2.....	245
7.2.1.4	Phagocytosis and TLR Function.....	246
7.2.2	NOD Intracellular Receptors for Pathogens.....	246
7.2.3	Toll Polymorphism and the Hygiene Hypothesis....	246
7.3	Host Antimicrobial Peptides	247
7.3.1	General Properties.....	247
7.3.2	Defensins and Cathelicidins	248
7.3.2.1	Defensins	248
7.3.2.2	Cathelicidin or hCAP18	249
7.3.3	Dermaseptins and Frog Peptides.....	250
7.3.4	Bactericidal/Permeability-Increasing Protein	251
7.3.5	Lactoferrin, Lactoferricin, and Talactoferrin	252
7.4	Functions of Antimicrobial Peptides.....	253
7.4.1	Antibacterial Activity.....	253
7.4.2	Anticancer Activity of AMPs.....	253
7.5	In Vivo Applications and Human-Trials of AMPs.....	255
7.5.1	General Considerations	255
7.5.2	Burns Injury, Wound Healing	256
7.5.3	Cancer Therapy	256
7.5.4	Infant Diarrhea.....	257
7.5.5	<i>Helicobacter pylori</i> -Related Ulcers	257
7.5.6	Hepatitis C Treatment.....	258
7.5.7	Oral Mucositis	258
7.5.8	Ventilator-Associated Pneumonia	258
7.5.9	Sepsis and Endotoxemia.....	259
7.6	Summary and Conclusions.....	260
	Appendices	261
	References	265

Chapter 8	Anabolic Dysfunction	275
8.1	Introduction	275
8.1.1	Anabolic–Catabolic Imbalance.....	275
8.1.2	Anabolic Dysfunction Allied to Nutrient and Hormone Resistance.....	275
8.1.3	Protein Synthesis and Breakdown during Illness	277
8.2	Insulin and Muscle Protein Metabolism	278
8.2.1	Insulin Signaling	279
8.2.2	Insulin Resistance of Glucose Metabolism.....	281
8.2.3	Insulin Resistance of Muscle Protein Metabolism.....	282
8.2.4	Insulinotropic Bioactive Peptides.....	283
8.3	Growth Hormone and IGF-1	285
8.3.1	Properties of Growth Hormone and IGF-1	286
8.3.2	Growth Hormone Receptor Signal Transduction....	286
8.3.3	Biological Effects of Growth Hormone/IGF-1 Axis	287
8.3.4	Growth Hormone Resistance	287
8.4	Growth Hormone Secretagogues.....	289
8.4.1	Growth Hormone Release Peptides.....	289
8.4.2	Hexarelin and Alexamorelin	290
8.4.3	Ghrelin.....	292
8.5	Leucine, BCAA, and Related Peptides.....	294
8.5.1	Essential Amino Acids as Anabolic Agents	294
8.5.2	The Branched-Chain Amino Acids	294
8.5.3	Leucine	295
8.5.4	Whey Protein and Peptides	295
8.6	In Vivo Applications and Clinical Trials.....	296
8.6.1	Short Bowel Syndrome.....	296
8.6.2	HIV Patients	298
8.6.3	Chronic Renal Failure	300
8.6.4	Critical Illness and Sepsis	300
8.6.5	Cancer Cachexia and Muscle Wasting	301
8.6.6	Liver Disease	302
8.6.7	Adverse Effects and Safety Concerns	303
	References	304

Chapter 9	Bioactive Peptides for Alleviating Illness Anorexia	323
9.1	Illness Anorexia.....	323
9.1.1	Models for the Regulation of Food Intake	323
9.1.2	Bioactive Peptides and Energy Homeostasis.....	325
9.1.3	Anorectic Bioactive Peptides.....	325
9.1.4	Serotonin	326
9.1.5	Cytokines and Food Intake	327
9.2	Leptin and Food Intake	327
9.2.1	Characteristics of Leptin Receptor Signaling	327
9.2.2	Leptin Regulation of Food Intake	328
9.2.3	Leptin Resistance during Obesity	329
9.2.4	Leptin Role in Illness Anorexia	330
9.3	Melanocortin Peptides	331
9.3.1	Melanocyte-Stimulating Hormone.....	331
9.3.2	Melanocortin Networks to Leptin and Serotonin Signaling.....	331
9.3.3	Melanocortin Receptors	331
9.3.4	Peptide Agonists and Antagonists for Melanocortin Receptors	334
9.4	Ghrelin.....	337
9.4.1	Characteristics of Ghrelin	337
9.4.2	The Ghrelin Receptor.....	337
9.4.3	Factors Affecting Ghrelin Release	337
9.4.3.1	Ghrelin Circadian and Ultradian Rhythms.....	340
9.4.3.2	Food Intake	341
9.4.3.3	Macronutrient Composition.....	341
9.4.3.4	Hormones and Ghrelin Secretion	341
9.4.3.5	Ghrelin and Obesity.....	342
9.4.3.6	Fasting Weight Loss.....	342
9.4.3.7	Aging and Ghrelin Secretion	343
9.4.3.8	Cachexia	344
9.4.4	Exogenous Ghrelin and Food Intake.....	345
9.4.5	Mode of Ghrelin Orexigenic Action	346
9.5	Other Bioactive Peptides for Moderating Appetite	346
9.5.1	Agouti-Signaling Protein and AgRP	347
9.5.2	Neuropeptide Y	348
9.5.3	Serotonin Antagonists	348
9.5.4	Dietary Proteins and Satiety	349
9.6	In Vivo Studies and Controlled Trials.....	351
9.6.1	Cancer Anorexia.....	351
9.6.2	Pulmonary Obstructive Disease.....	352
9.6.3	Chronic Kidney Failure and Dialysis Patients	352
9.6.4	HIV Infection Anorexia	353

9.6.5 Melanocortin Antagonists for Anorexia Treatment.....	353
9.7 Summary and Conclusions.....	354
References	355
Index.....	369