
**OVERWEIGHT AND THE
METABOLIC SYNDROME:
FROM BENCH TO BEDSIDE**

ENDOCRINE UPDATES

Shlomo Melmed, M.D., Series Editor

- J.A. Fagin (ed.): Thyroid Cancer. 1998. ISBN: 0-7923-8326-5
- J.S. Adams and B.P. Lukert (eds.): Osteoporosis: Genetics, Prevention and Treatment. 1998. ISBN: 0-7923-8366-4.
- B.-Å. Bengtsson (ed.): Growth Hormone. 1999. ISBN: 0-7923-8478-4
- C. Wang (ed.): Male Reproductive Function. 1999. ISBN: 0-7923-8520-9
- B. Rapoport and S.M. McLachlan (eds.): Graves' Disease: Pathogenesis and Treatment. 2000. ISBN: 0-7923-7790-7.
- W.W. de Herder (ed.): Functional and Morphological Imaging of the Endocrine System. 2000. ISBN 0-7923-7923-9
- H.G. Burger (ed.): Sex Hormone Replacement Therapy. 2001. ISBN 0-7923-7965-9
- A. Giustina (ed.): Growth Hormone and the Heart. 2001. ISBN 0-7923-7212-3
- W.L. Lowe, Jr. (ed.): Genetics of Diabetes Mellitus. 2001. ISBN 0-7923-7252-2
- J.F. Habener and M.A. Hussain (eds.): Molecular Basis of Pancreas Development and Function. 2001. ISBN 0-7923-7271-9
- N. Horseman (ed.): Prolactin. 2001. ISBN 0-7923-7290-5
- M. Castro (ed.): Transgenic Models in Endocrinology. 2001 ISBN 0-7923-7344-8
- R. Bahn (ed.): Thyroid Eye Disease. 2001. ISBN 0-7923-7380-4
- M.D. Bronstein (ed.): Pituitary Tumors in Pregnancy ISBN 0-7923-7442-8
- K. Sandberg and S.E. Mulroney (eds.): RNA Binding Proteins: New Concepts in Gene Regulation. 2001. ISBN 0-7923-7612-9
- V. Goffin and P.A. Kelly (eds.): Hormone Signaling. 2002 ISBN 0-7923-7660-9
- M.C. Sheppard and P.M. Stewart (eds.): Pituitary Disease. 2002 ISBN 1-4020-7122-1
- N. Chattopadhyay and E.M. Brown (eds.): Calcium-Sensing Receptor. 2002. ISBN 1-4020-7314-3
- H. Vaudry and A. Arimura (eds.): Pituitary Adenylate Cyclase-Activating Polypeptide. 2002. ISBN 1-4020-7306-2
- R.C. Gaillard (ed.): The ACTH AXIS: Pathogenesis, Diagnosis and Treatment. 2003. ISBN 1-4020-7563-4
- P. Beck-Peccoz (ed.): Syndromes of Hormone Resistance on the Hypothalamic-Pituitary-Thyroid Axis. 2004. ISBN 1-4020-7807-2
- E. Ghigo (ed.): Ghrelin. 2004. ISBN 1-4020-7770-X
- C.B. Srikant (ed.): Somatostatin. 2004. ISBN 1-4020-7799-8
- V.D. Castracane and M.C. Henson (eds.): Leptin. 2006. ISBN 0-387-31415-6
- G.A. Bray and D.H. Ryan (eds.): Overweight and the Metabolic Syndrome. 2006. ISBN 0-387-32163-2

OVERWEIGHT AND THE METABOLIC SYNDROME: FROM BENCH TO BEDSIDE

Edited by

George A. Bray, MD

*Pennington Biomedical Research Center
Louisiana State University System
Baton Rouge, Louisiana, USA*

Donna H. Ryan, MD

*Pennington Biomedical Research Center
Louisiana State University System
Baton Rouge, Louisiana, USA*



Springer

George A. Bray, MD
Pennington Biomedical Research Center
Louisiana State University
6400 Perkins Road
Baton Rouge, LA, USA

Donna H. Ryan, MD
Pennington Biomedical Research Center
Louisiana State University
6400 Perkins Road
Baton Rouge, LA, USA

**OVERWEIGHT AND THE METABOLIC SYNDROME:
FROM BENCH TO BEDSIDE**

Library of Congress Control Number: 2006922024

ISBN-10: 0-387-32163-2 e-ISBN-10: 0-387-32164-0

ISBN-13: 978-0387-32163-9 e-ISBN-13: 978-0387-32164-6

Printed on acid-free paper.

© 2006 Springer Science+Business Media, LLC

All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer Science+Business Media, Inc., 233 Spring Street, New York, NY 10013, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden.

The use in this publication of trade names, trademarks, service marks and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.

While the advice and information in this book are believed to be true and accurate at the date of going to press, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed in the United States of America.

9 8 7 6 5 4 3 2 1

springer.com

Contents

Preface	xv
Contributors	xix
Chapter 1: Neuroendocrine Control of Food Intake	
<i>Andrew A. Butler, James L. Trevaskis and Christopher D. Morrison</i>	1
1. Introduction	1
2. Central Nervous System Regulation of Feeding Behavior	2
3. Neuroendocrine Factors Secreted from the Gut	2
3.1. Cholecystokinin	3
3.2. Peptide YY	5
3.3. Ghrelin	6
3.4. Amylin	7
3.5. Enterostatin	7
3.6. Glucagon-like Peptide	8
3.7. Bombesin Family: Bombesin, Gastrin-releasing Peptide and Neuromedin B	8
3.8. Oxyntomodulin	9
3.9. Leptin	10
4. Neuroendocrine Indicators of Long-term Energy Balance: Leptin and Insulin	10
4.1. Leptin and Insulin Signaling in Diet-induced Obesity	12
5. Summary	13
References	13
Chapter 2: Body Composition Assessment of Obesity	
<i>Wm. Cameron Chumlea</i>	23
1. Introduction	23
2. Overview of Body Composition Methods	24
2.1. Anthropometry	24
2.2. Weight and Stature	24
2.3. Body Mass Index	25
2.4. Abdominal Circumference	26
2.5. Skinfolds	27
2.6. Bioelectric Impedance Analysis	28

2.7. Body Density	29
2.8. Total Body Water	29
2.9. Dual-energy x-ray Absorptiometry	29
3. Ethnic Differences in Body Composition	30
4. Available Reference Data	30
5. Recommendations	31
6. Conclusion	31
Acknowledgments	32
References	32
 Chapter 3: Prevalence of Obesity and the Metabolic Syndrome	
<i>Ali H. Mokdad and Earl S. Ford</i>	37
1. Overweight and Obesity	37
2. Prevention and Control Programs	44
3. THE Metabolic Syndrome	45
4. Preventive and Control Strategies	47
5. Future Perspectives	48
References	49
 Chapter 4: The Genetic Contribution to Obesity	
<i>Raul A. Bastarrachea, Jack W. Kent Jr., Jeff T. Williams, Guowen Cai, Shelley A. Cole and Anthony G. Comuzzie</i>	55
1. Introduction	55
2. Obesity as a Common Complex Phenotype	56
3. Ancient Genes in a Modern World: An Evolutionary Genetic Perspective on Obesity	57
4. Approaches to Obesity Gene Discovery	58
4.1. Candidate Gene Association Study	59
4.2. Genome Scan	59
4.3. mRNA	60
5. Evidence from Animal Models for the Genetic Contribution to Obesity	60
5.1. Monogenic Obesity	60
5.2. Oligogenic Obesity	62
6. Evidence for the Genetic Contribution to Obesity in Humans	63
6.1. The Genetic Contribution to Rare Forms of Human Obesity	63
6.2. Genetic Contribution to Common Human Obesity	66
7. Conclusion	72
Acknowledgments	73
References	73

Chapter 5: Etiology of Obesity: The Problem of Maintaining Energy Balance

Barry E. Levin and Deborah J. Clegg 83

1. Introduction: Obesity and the Concept of Defended Body Weight 83
2. Neural Control of the Defended Body Weight 85
3. Obesity and the Problem of Maintaining Body Weight 88
4. How Is Body Weight Really Regulated? 90
5. Factors That Lower the Defended Body Weight 91
6. Implications for Future Research 91
- References 92

Chapter 6: Current Views of the Fat Cell as an Endocrine Cell: Lipotoxicity

Tamara Tchkonina, Barbara E. Corkey and James L. Kirkland 105

1. Introduction 105
2. Functions of Fat Tissue 105
3. Conditions Associated with Lipotoxicity 106
4. Mechanisms of Lipotoxicity 108
5. Inherent Properties of Cells Contribute to Susceptibility to Lipotoxicity 111
6. Association between Lipids and Inflammatory Responses 111
7. Mechanisms of Defense against Lipotoxicity 112
8. Preadipocytes and Fat Cells Are more Resistant than Other Cell Types to FA 114
9. Summary 116
10. Conclusions 117
- Acknowledgments 118
- References 118

Chapter 7: Ectopic Fat and the Metabolic Syndrome

Frederico G.S. Toledo and David E. Kelley 125

1. Introduction 125
2. Consequences of Excess Adiposity to Whole-body Glucose Homeostasis 126
3. FFA-induced Insulin Resistance 127
4. Ectopic Fat in Skeletal Muscle and Insulin Resistance 128
5. Relationships between Ectopic Fat in Liver and Insulin Resistance 129
6. Human Lipodystrophic Syndromes 130
7. Concluding Remarks 131
- References 132

Chapter 8: Abdominal Obesity and the Metabolic Syndrome

Jean-Pierre Després, Isabelle Lemieux and Natalie Alm  ras 137

1. Introduction 137
2. Metabolic Syndrome without Hyperglycemia Predicts an Increased CHD Risk 140

3.	Why Measure Waist Circumference as well and not just BMI?	141
4.	Abdominal Obesity: The Driving Force behind the Metabolic Syndrome?	143
5.	The Metabolic Syndrome: Is Waist Girth Sufficient?	143
6.	Are NCEP-ATP III Criteria Valid in All Populations?	144
7.	Managing CHD Risk in Patients with the Metabolic Syndrome: What Should Be Our Goal?	145
8.	Summary	146
	Acknowledgments	148
	References	148

Chapter 9: The Problems of Childhood Obesity and the Metabolic Syndrome

Sonia Caprio and Ram Weiss 153

1.	Introduction	153
2.	Prevalence of the Metabolic Syndrome in Children and Adolescents: Impact of Obesity	154
3.	Effects of Insulin Resistance (HOMA-IR) on the Prevalence of the Metabolic Syndrome	155
4.	Proinflammatory and Antiinflammatory Markers and Insulin Resistance	158
5.	Pathophysiological Studies of the Prediabetic Phenotype in Youth	159
6.	Relationship between Insulin Resistance and Tissue Lipid Partitioning	160
7.	Early Reduction of β -cell Sensitivity to Glucose in Obese Youth with Impaired Glucose Tolerance	162
8.	Longitudinal Study of Changes in Glucose Tolerance Status in Obese Youth	164
	Acknowledgments	165
	References	165

Chapter 10: Evaluation of the Overweight and Obese Patient

George A. Bray and Donna H. Ryan 169

1.	Introduction	169
2.	Definitions	170
3.	Anthropometric Measures	170
3.1.	Height and Weight	170
3.2.	Waist Circumference	170
4.	Instrumental Methods for Measuring Body Fat	171
4.1.	Dual X-ray Absorptiometry	172
4.2.	Density	172
4.3.	Isotope Dilution	173
4.4.	Bioelectric Impedance	173
5.	Imaging Techniques for Body Composition	173
6.	Summary of Clinical Recommendations for Measurement of Body Composition	173
7.	Body Fat through the Life Span	173
8.	Prevalence of Overweight	174

9.	Clinical Evaluation of Overweight Patients	176
9.1.	Body Mass Index	176
9.2.	Waist Circumference	178
9.3.	Weight Gain	178
9.4.	Sedentary Lifestyle	178
9.5.	Laboratory and Other Measures	179
10.	The Metabolic Syndrome	179
11.	Etiologic Factors Underlying Obesity	180
12.	Introduction to Treatment: Risk–Benefit Assessment	183
13.	Conclusion	183
	References	184

Chapter 11: Dietary Approaches to Obesity and the Metabolic Syndrome

	<i>Gary D. Foster and Angela P. Makris</i>	187
1.	Introduction	187
2.	Low-fat Diets	188
2.1.	Efficacy of Low-fat Diets on Weight Loss, Hypertension, and Diabetes	188
3.	Very-low-fat Diets	191
3.1.	Efficacy of Very-low-fat Diets on Weight Loss and Cardiovascular Disease	191
4.	Moderate-fat Diets	192
4.1.	Efficacy of Moderate-fat Diets on Weight Loss, Cardiovascular Disease, and Diabetes	193
5.	The High-protein Diet	195
5.1.	Efficacy of High-protein Diets on Weight Loss	196
6.	Low-carbohydrate Diets	198
6.1.	Efficacy of Low-carbohydrate Diets on Weight Loss, Insulin Sensitivity, and Lipids	198
7.	Low Glycemic Index Diet	202
7.1.	Effects of Low Glycemic Index Diets on Hunger and Weight Loss and Insulin Sensitivity	202
8.	Clinical Implications and Future Directions for Research	205
	References	205

Chapter 12: Exercise as an Approach to Obesity and the Metabolic Syndrome

	<i>John M. Jakicic and Amy D. Otto</i>	211
1.	Introduction	211
2.	Effect of Exercise on Health-related Parameters	211
3.	Impact of Exercise on Weight Loss	213
4.	Exercise Prescription Considerations for Long-term Weight Control	214
5.	Summary	216

Acknowledgments	216
References	216

Chapter 13: Behavioral Strategies for Controlling Obesity

Donald A. Williamson, Corby K. Martin and Tiffany M. Stewart 219

1. Introduction	219
2. History of Behavioral Strategies for Controlling Obesity	220
2.1. Philosophy of Treatment	220
3. Behavioral Treatment for Adults	221
3.1. Approach and Outcomes	221
3.2. Duration of Treatment	221
3.3. Targets and Tools	221
3.4. Weight Maintenance Strategies	225
3.5. Special Considerations	226
4. Behavioral Treatment for Children and Adolescents	227
4.1. Approaches, Tools, and Outcomes	227
4.2. Reinforcement, Adherence, and Behavior Change	227
4.3. Social Support and Parent Training	228
4.4. Problem-solving	228
4.5. Meal Planning	228
4.6. Physical Activity	229
4.7. Special Considerations	229
5. Conclusions	230
6. Summary	230
References	231

Chapter 14: Obesity Prevention

Shiriki K. Kumanyika and Stephen R. Daniels 233

1. Introduction	233
2. Defining the Task	234
2.1. Individual Level Perspective	234
2.2. Population Perspective	235
2.3. Goals and Priorities	235
3. Population-wide Approaches	237
3.1. Initiatives Related to Food	238
3.2. Initiatives Related to Physical Activity	238
3.3. Social Marketing	239
4. Prevention Targeted to Selected Population Groups	239
4.1. Adults	240
4.2. Children	243
5. Individually Targeted Approaches	247
6. Multilevel Approaches	247

7.	Methodological Considerations	248
8.	Conclusion	249
	Note	249
	References	249

Chapter 15: Orlistat and Sibutramine in the Management of Obesity

Holly Wyatt 255

1.	Introduction	255
2.	Who Is Appropriate? Criteria for Use of Weight Loss Medications	255
3.	Why Do Health Care Providers Choose not to Use Weight Loss Medications?	257
4.	What Weight Loss Drugs Are Available?	258
5.	How Should Weight Loss in Medication Clinical Trials Be Evaluated?	259
6.	Sibutramine	260
	6.1. Mechanism of Action	261
	6.2. Therapeutic Potential for Obesity	261
	6.3. Efficacy in Weight Loss Maintenance	262
	6.4. Efficacy in Managing Obesity-related Risk Factors	264
	6.5. Tolerability and Safety	265
	6.6. Special Considerations when Prescribing Sibutramine	266
7.	Orlistat	266
	7.1. Mechanism of Action	267
	7.2. Therapeutic Potential for Obesity	267
	7.3. Efficacy in Weight Loss Maintenance	270
	7.4. Efficacy in Managing Obesity-related Risk Factors	270
	7.5. Tolerability and Safety	271
	7.6. Special Considerations when Prescribing Orlistat	272
8.	The Future of Weight Loss Medications	272
	8.1. Sibutramine and Orlistat Usage in Adolescents	272
	8.2. Combination Therapy	273
	8.3. Continuous vs. Episodic Medication Usage	273
9.	Summary	274
	References	274

Chapter 16: A Status of Drugs on the Horizon for Obesity and the Metabolic Syndrome—a Comprehensive Review 2005

Frank Greenway and George Bray 281

1.	Introduction	281
2.	Drugs Approved for Indications Other than Obesity and That Cause Weight Loss	282
	2.1. Bupropion	282
	2.2. Fluoxetine/Sertraline	283
	2.3. Zonisamide	284
	2.4. Topiramate	284

2.5.	Metformin	285
2.6.	Somatostatin	286
2.7.	Pramlintide	287
2.8.	Exenatide	287
3.	Drugs in Phase III Clinical Trials with no Approval	288
3.1.	Rimonabant	288
3.2.	Axokine	289
3.3.	Leptin	289
4.	Drugs in the Early Phases of Development	290
4.1.	Growth Hormone Fragment	290
4.2.	Cholecystokinin	290
4.3.	PYY 3-36	290
4.4.	Oleoylestrone	291
4.5.	Serotonin 2C Receptor Agonist	291
4.6.	Neuropeptide Y Receptor Antagonists	291
4.7.	Melanin Concentrating Hormone Receptor-1 Antagonist	292
4.8.	Pancreatic Lipase Inhibitor	292
4.9.	Glucagon-like Peptide-1 Agonists and Dipeptidyl Peptidase-4 Inhibitors	292
5.	Drugs no Longer under Investigation or Withdrawn	293
5.1.	β 3-adrenergic Agonists	293
5.2.	Ephedra	293
5.3.	Phenylpropanolamine	294
5.4.	Bromocriptine	294
5.5.	Ecopipam	295
6.	New Areas where Drugs Are Being Developed	295
6.1.	Histamine-3 Receptor Antagonists	295
6.2.	Ghrelin Antagonist	295
6.3.	11 β -hydroxysteroid Dehydrogenase Type I Inhibitor	295
6.4.	Modulators of Energy Sensing in the Brain (Acetyl Co-A Carboxylase 2 Inhibitor; Fatty Acid Synthase; Carnitine Palmitoyltransferase-3)	296
6.5.	Adiponectin	296
6.6.	Melanocortin-4 Receptor (MC4R) Agonists	296
7.	Natural Products (over-the-counter Preparations)	297
7.1.	Chromium	297
7.2.	<i>Garcinia cambogia</i>	297
7.3.	Chitosan	298
7.4.	<i>Hoodia</i>	298
7.5.	<i>Stevia</i>	298
7.6.	<i>Citrus aurantium</i>	299
8.	Summary and Conclusions	299
	References	300

Chapter 17: Surgical Treatment of the Overweight Patient	
<i>George A. Bray</i>	307
1. Introduction	307
2. Surgical Approaches to Obesity and Their Historical Context	309
3. Indications and Contraindications	310
3.1. Indications in Adults	310
3.2. Contraindications for Adults	310
3.3. Bariatric Surgery for the Pediatric Age Group	311
4. Effectiveness of Surgical Procedures	312
5. Mechanisms for Weight Loss	315
6. Benefits from Bariatric Surgery	316
7. Complications Associated with Bariatric Surgery	318
7.1. Complications Following Lap-band Bariatric Surgery	318
7.2. Complications Following Restrictive Bariatric Surgery	318
7.3. Complications with Malabsorptive Operations	319
8. Other Operative Procedures for the Overweight Patient	321
8.1. Intra-gastric Balloon	321
8.2. Gastric Stimulation or Gastric Pacing	321
8.3. Liposuction and Omentectomy	321
9. Summary	322
References	323
Index	329

Preface

The field of obesity and the metabolic syndrome continues to advance on all fronts. This book is an effort to bring together a series of chapters that cover many of the newer facets of the problem. We have tried to capture the goal of this book in the subtitle “from bench to bedside”. Fundamentally, as human biologists, we are interested in understanding the problem of obesity and the metabolic syndrome and then applying this new knowledge to easing the burden of people afflicted in this disease state. We begin with the laboratory findings. Butler and his colleagues begin the process with an illuminating discussion of the factors that control the termination of meals. After a brief review of the neuroendocrine control system, they provide a detailed look at the gastrointestinal and pancreatic factors that can stimulate or inhibit food intake. They then look at the long-term control affected by leptin and insulin. In the next chapter, Dr. Chumlea discusses the various methods for measuring “obesity”. Dual-energy absorptiometry (DXA) has the ability to provide estimates of fat mass, lean mass and bone mass making it quite versatile. However, from a practical perspective, weight, waist circumference and the body mass index (body weight in kg divided by the square of height in meters) are the most useful. The body mass index (BMI) has been the most widely used index in the assessment of the current changes in prevalence of obesity, providing a good picture of the increasing epidemic of obesity. The progress of this epidemic has been well characterized by Dr. Mokdad from the Centers for Disease Control and Prevention, the U.S. Governmental agency charged with tracking this epidemic. Genetic factors are clearly behind the susceptibility to obesity that characterizes this epidemic. Dr. Comuzzie, who has contributed important information to this problem, focuses on the advances that we have experienced in understanding the relations of nature and nurture. In a well written and timely chapter, Drs. Levin and Clegg argue the case of a “set-point” or a defended body weight. They begin with the historical and anatomic data and the move to discussing the intricacies of the mechanisms that control this process. Fat is the site for storage of extra energy. When the fat cells reach their maximum storage capacity, new fat cells may be recruited, but fat may also be stored ectopically in other organs. Tchkonja, Corkey, Kirkland explore this important new concept in a chapter dealing with lipotoxicity. The conditions for lipotoxicity occur when net capacity to store and utilize lipids is exceeded in diseases

such as diabetes, obesity, the metabolic syndrome, indexmetabolic syndrome lipodystrophies, aging, and other conditions. The chapter by Toledo and Kelley extends this concept of lipotoxicity to the issues associated with visceral adipose tissue. This ectopic storage of fat is associated with insulin resistance. This group has coined the term “metabolic inflexibility” to describe the setting in which an infusion of insulin fails to enhance carbohydrate metabolism in muscle. They develop the “portal hypothesis” which suggests that visceral adipose tissue provides fatty acids to the liver than lead to accumulation of lipid there and in the intramyocellular compartment. Fatty-acyl-CoAs, diacylglycerol and ceramides are important candidates for these metabolic changes. As demonstrated by several groups, this effect is associated with changes in mitochondrial genes and their enzymes that are involved in oxidative phosphorylation. Finally, they discuss the lipodystrophic states where loss of fat is associated with increased insulin resistance. Recent studies show that replacing leptin, a product of the fat cell, to individuals with too little fat can ameliorate most of the metabolic features of lipodystrophy. Drs. Lemieux and Despres, leaders in the field of studying visceral adipose tissue and the metabolic syndrome provide a succinct summary of the advances in this area. Children who become overweight bear the stigma associated with obesity, and at the same time experience the detrimental health benefits that are often seen. Caprio and Weiss, who have been leaders in establishing criteria for the metabolic syndrome in adolescents, review their data and the types of changes that characterize this condition in the adolescents in their clinic. From the laboratory side of the problem, we now turn to translating these findings into the evaluation and treatment of obesity and the metabolic syndrome. Evaluating any patient is the first step in deciding how serious the problem may be and what steps to take in correcting it. Ryan and Bray provide the introductory steps in this process with a chapter dealing with evaluation of the patient with obesity and the metabolic syndrome. It is now clear that measurement of waist circumference along with the BMI provide the first steps. For establishing the metabolic syndrome other measurements such as blood pressure, a lipid panel and glucose are needed. If two of these are abnormal and there is an enlarged waist one can diagnose the metabolic syndrome. Once the diagnosis is made, treatment is in order. Since all of the components of this syndrome will respond positively to weight loss, strategies to help people lose weight are the first steps. However, when the lipid, blood pressure or glucose abnormalities remain abnormal, they should be treated with one of the appropriate therapies. Lifestyle strategies are the first line of approach. Diet, exercise and behavioral therapy make up the 3 components of these lifestyle approaches. Diet is the first line of attack and the chapter by Foster and Makris introduces us to this problem. Their chapter provides a nice review of the low carbohydrate diets in comparison with other diets. Foster and Makris first review the low and moderate fat diets and the turn

to the low carbohydrate diets and provide us a feeling for the value that each of these groups of diets have in the treatment of overweight. Diets reduce energy intake and thus require overweight individuals to draw fat from their fat stores. Exercise, reviewed by Jakicic and Otto, works by increasing the utilization of energy through physical exertion. They begin by convincing us that those who are more active have improved health benefits and longevity. They then review the literature on weight loss studies and show that exercise alone is not a very effective strategy. However, for maintaining weight loss, becoming and remaining more active clearly plays a central role. The third arm of lifestyle is behavior therapy whose role is reviewed in a chapter by Williamson, Stewart and Martin. They provide an historical background and then describe the many features that come under this category. The use of portion controlled foods and the use of the internet are two of the more recent advances, each of which offers the hope of extending the scope and success of this approach. Obviously we would prefer to prevent overweight than to have to treat it. Kumanyika and Daniels take us through the literature on studies that have attempted to prevent the progression of overweight. Two broad kinds of approaches have been taken—population wide approaches and targeted approaches. In spite of much work, the authors correctly note that at present we have no definitive studies to guide a clear approach to the problem. Where prevention fails, therapy is needed. Two drugs are currently approved by the U.S. Food and Drug Administration for treatment of obesity. Dr. Wyatt discusses the use of these two drugs, sibutramine and orlistat. Although both are effective in producing weight loss, the loss is moderate and often frustrating to the participant who is taking the drug. Although only 2 drugs are currently approved, Greenway and Bray review the burgeoning new drug armamentarium. Several drugs approved for use in diabetes, like metformin, pramlintide and exenatide produce weight loss. Rimonabant, an antagonist to the cannabinoid CB1 receptors in the brain is a promising new agent that will soon be evaluated by the FDA for approval and clinical use. There is cautious optimism that it may change the landscape of treatment for those individuals whose overweight has not been prevented. The final chapter deals with surgical interventions for overweight patients. Since laparoscopic techniques for this procedure became wide spread, its performance and safety have both changed significantly. Over 100,000 operations were performed last year, and the number continues to rise. With this final chapter, we complete our tour from laboratory to clinic. We hope it meets the needs for which it was put together—a survey of new strategies to bring the laboratory to the clinic for treatment of obesity and the metabolic syndrome.

George A. Bray, M.D.

Contributors

1. Natalie Alméras
Laval Hospital Research Center, Laval Hospital, Ste-Foy, Québec, Canada
2. Raul A. Bastarrachea
Department of Genetics, Southwest Foundation for Biomedical Research,
San Antonio, TX, USA
3. George A. Bray
Pennington Biomedical Research Center, Baton Rouge, LA, USA
4. Andrew A. Butler
Pennington Biomedical Research Center, Louisiana State University Sys-
tem, Baton Rouge, LA, USA
5. Guowen Cai
Department of Genetics, Southwest Foundation for Biomedical Research,
San Antonio, TX, USA
6. Sonia Caprio
Department of Pediatrics and the Children's General Clinical Research
Center, Yale University School of Medicine, New Haven, CT, USA
7. Wm. Cameron Chumlea
Departments of Community Health and Pediatrics, Lifespan Health Re-
search Center, Wright State University School of Medicine, Dayton, OH,
USA
8. Deborah J. Clegg
Department of Psychiatry, Genome Research Institute, Cincinnati, OH,
USA
9. Shelley A. Cole
Department of Genetics, Southwest Foundation for Biomedical Research,
San Antonio, TX, USA
10. Anthony G. Comuzzie
Department of Genetics, Southwest Foundation for Biomedical Research,
San Antonio, TX, USA
11. Barbara E. Corkey
Obesity Center, Evans Department of Medicine, Boston University,
Boston, MA, USA

12. Stephen R. Daniels
Departments of Pediatrics and Environmental Health, Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine, Cincinnati, OH, USA
13. Jean-Pierre Després
Québec Heart Institute, Laval Hospital Research Center, Laval Hospital, Ste-Foy, Québec, Canada and
Department of Social and Preventive Medicine, Laval University, Ste-Foy, Québec, Canada
14. Earl S. Ford
Centers for Disease Control and Prevention, Atlanta, GA, USA
15. Gary D. Foster
University of Pennsylvania School of Medicine, Philadelphia, PA, USA
16. Frank Greenway
Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, USA
17. John M. Jakicic
Department of Health and Physical Activity, Physical Activity and Weight Management Research Center, University of Pittsburgh, Pittsburgh, PA, USA
18. David E. Kelley
Division of Endocrinology and Metabolism, Department of Medicine, University of Pittsburgh, School of Medicine, Pittsburgh, PA, USA
19. Jack W. Kent Jr.
Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio, TX, USA
20. James L. Kirkland
Obesity Center, Evans Department of Medicine, Boston University, Boston, MA, USA
21. Shiriki K. Kumanyika
Department of Biostatistics and Epidemiology, Department of Pediatrics, and Graduate Program in Public Health Studies, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
22. Isabelle Lemieux
Québec Heart Institute, Laval Hospital Research Center, Laval Hospital, Ste-Foy, Québec, Canada
23. Barry E. Levin
Department of Neurology and Neurosciences, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA and Neurology Service, VA Medical Center, NJ, USA
24. Angela P. Makris
University of Pennsylvania School of Medicine, Philadelphia, PA, USA

25. Corby K. Martin
Pennington Biomedical Research Center, Baton Rouge, LA, USA
26. Ali H. Mokdad
Centers for Disease Control and Prevention, Atlanta, GA, USA
27. Christopher D. Morrison
Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, USA
28. Amy D. Otto
Department of Health and Physical Activity, Physical Activity and Weight Management Research Center, University of Pittsburgh, Pittsburgh, PA, USA
29. Donna H. Ryan
Pennington Biomedical Research Center, Baton Rouge, LA, USA
30. Tiffany M. Stewart
Pennington Biomedical Research Center, Baton Rouge, LA, USA
31. Tamara Tchkonia
Obesity Center, Evans Department of Medicine, Boston University, Boston, MA, USA
32. Frederico G.S. Toledo
Division of Endocrinology and Metabolism, Department of Medicine, University of Pittsburgh, School of Medicine, Pittsburgh, PA, USA
33. James L. Trevaskis
Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, USA
34. Ram Weiss
Department of Pediatrics and the Children's General Clinical Research Center, Yale University School of Medicine, New Haven, CT, USA
35. Jeff T. Williams
Southwest National Primate Research Center, San Antonio, TX, USA
36. Donald A. Williamson
Pennington Biomedical Research Center, Baton Rouge, LA, USA
37. Holly Wyatt
University of Colorado at Denver and Health Sciences Center, Denver, CO, USA

Chapter 1

Neuroendocrine Control of Food Intake

Andrew A. Butler, James L. Trevaskis and Christopher D. Morrison

*Pennington Biomedical Research Center, Louisiana State University System,
6400 Perkins Road, Baton Rouge, LA 70808, USA*

1. INTRODUCTION

Most organisms function in environments with marked seasonal and, on a less predictable basis, climactic changes in nutrient availability. Species survival is dependent on systems that are remarkably adept at balancing food intake with the fluctuations in energy expenditure and with the amount of energy stored as triacylglycerol (TAG) in adipocytes. Neural and endocrine regulatory systems affecting feeding behavior must respond to short-term cues, such as the ability to sense and respond to stomach contents, along with signals concerning the long-term status of energy balance over periods of days. Feeding behavior is also linked to the circadian cycle, with the circadian rhythms of feeding behavior recently suggested to be critical for maintaining normal body weight [1].

The problem currently facing the global community is that, faced with an abundance of calories and diminished requirements for physical activity, a significant portion of the population are unable to maintain energy balance, leading to increased fat mass. Investigation of experimental rodent models strongly suggests that excess consumption of calories, especially associated with high-fat diets, is a significant factor causing obesity and insulin resistance [2, 3]. The latter is the defining feature of the insulin resistance syndrome, formerly called syndrome X or the metabolic syndrome, and comprises a cluster of diseases including type 2 diabetes, hypertension, and cardiovascular disease [4]. In the face of an epidemic of obesity and insulin resistance syndrome, there is enormous interest by pharmaceutical and academic groups to elucidate mechanisms that regulate food intake as a means to develop effective therapies against obesity and insulin resistance. This chapter describes the current models for the regulation of food intake by neuroendocrine factors, which integrate signals of long-term energy balance, involving primarily the adipokine leptin and leptin receptors expressed in the central nervous system (CNS), with factors secreted from the gut. Most of these factors have similar effects on energy balance whether administered peripherally or directly into areas of the CNS

known to regulate feeding behavior. This chapter therefore begins with a brief introduction to the CNS centers that control feeding behavior.

2. CENTRAL NERVOUS SYSTEM REGULATION OF FEEDING BEHAVIOR

Feeding is a complex behavior, involving the integration of a number of reward (hedonic) behaviors with the homeostatic systems that sense energy balance [5]. Within the CNS, areas distributed throughout the forebrain and caudal brain stem appear to be important for regulating feeding behavior [6, 7]. One area that appears to be particularly significant is the hypothalamus. Neurons in this area integrate sensory and endocrine signals into outputs that influence fluid and food intake; normal function of the hypothalamus is critical for energy homeostasis [8]. Hypothalamic neurons respond to several of the gut and adipocyte secreted factors known to affect food intake, with hypothalamic lesions sometimes severely abrogating the feeding response. While a comprehensive description of the hypothalamic neuronal circuitry involved in energy homeostasis is beyond the scope of this chapter, a list of some of the hypothalamic neurons identified as being important for the regulation of feeding behavior is provided in Table 1. Several excellent reviews of this topic have also recently been published [5, 6, 14–16].

The caudal brain stem is also an important site in regulating feeding behavior. Neurons within the nucleus tractus solitarius (NTS) and dorsal motor nucleus of the vagus (DMV) in the brain stem receive, and integrate, sensory inputs from vagal nerves involved in sensing the accumulation of nutrients in the stomach and duodenum tract through mechanical and chemical stimuli that include distension, changes in the gastrointestinal nutrient concentration, and changes in pH and osmolarity in the gut lumen [17]. The brain stem is also highly interconnected with the hypothalamus, communicating through ascending projections to regulate the response to fasting [7]. Conversely, descending projections from the hypothalamus to the brain stem may modulate the effectiveness of short-term satiety signals, such as cholecystokinin (CCK), in meal termination [18].

3. NEUROENDOCRINE FACTORS SECRETED FROM THE GUT

In addition to the mechanosensory inputs received by vagal afferents, the gut releases at least 10 circulating factors, some of which may act as satiety signals to the CNS [19]. Some of these gut factors are described in the following section. For some of these peptides, evidence for suppression of food

Table 1. Neurons that have been identified as critical for the normal regulation of energy homeostasis

Neuropeptides expressed	Location	Effect on feeding	Responds to	References
Proopiomelanocortin/cocaine and amphetamine-regulate transcript (POMC/CART)	Arcuate nucleus	Inhibitory	(+)-leptin, PYY _{3–36} , 5-HT, insulin, glucose, (–)-ghrelin	44, 46, 47, 49, 133–139
POMC	Nucleus tractus solitarius	Inhibitory	(+)-cholecystokinin (CCK)	140–142
Agouti-related peptide/neuropeptide Y (AgRP/NPY)	Arcuate nucleus	Stimulatory	(–)-leptin, PYY _{3–36} , insulin, (+)-ghrelin	44, 47, 133, 143
Melanin-concentrating hormone (MCH)	Lateral hypothalamic area	Stimulatory	(–)-leptin	144–148
Orexin	Lateral hypothalamic area	Stimulatory	(–)-leptin, glucose, ghrelin	12, 149

Orexin neurons innervate and regulate AgRP/NPY and POMC/CART neurons in the arcuate nucleus, indicating that these neurons might affect feeding behavior through regulating the hypothalamic melanocortin system [9, 10]. However, deletion of the *Orexin* gene, or ablation of orexin neurons, causes narcolepsy [11]. Orexin may primarily affect food intake by coordinating arousal with feeding [12, 13].

intake has only recently been described (e.g., amylin, glucagon-like peptide 1 [GLP-1], oxyntomodulin, peptide YY [PYY]), and for the case of PYY is still a matter of debate [20]. The administration of GLP-1 and PYY has been associated with the induction of illness-induced behavior, demonstrated by the induction of conditioned taste aversion in rodents [21–24]. These factors may therefore function not only as satiety signals, but possibly also as part of the stress response to visceral illness.

3.1. Cholecystokinin

Of all gut-derived satiety signals, the hormone cholecystokinin (CCK) is perhaps the most well-described hormone mediating satiety [25–27]. The role of CCK in meal termination was first demonstrated by Gibbs et al. in 1973 [28], and many subsequent studies have demonstrated that administration of CCK dose-dependently suppresses food intake. CCK is produced primarily by the enteroendocrine cells of the duodenal and jejunal mucosa, although CCK is also produced by both the enteric system and CNS [29]. These enteroendocrine cells are well positioned to sense the presence of nutrients within the gut, and indeed the secretion of CCK is stimulated by nutrient ingestion, with the

presence of fat or protein within the gut being the primary stimulus for CCK secretion [30]. CCK secretion is both rapid and short-lived, peaking within 30 minutes of meal ingestion, and in some species even more rapidly. This increase of CCK after nutrient ingestion serves two main purposes. The first is to act locally within the gut to enhance nutrient absorption, with CCK stimulating gallbladder contraction and also inhibiting gastric emptying [31, 32]. However, nutrient-induced secretion of CCK also acts to terminate individual meals, and this effect has been shown in many species including humans. CCK dose-dependently reduces food intake [28], but it is not a long-term regulator of body weight. Prolonged CCK administration does not effectively reduce body weight, and most individuals treated chronically with CCK compensate for the reduction in individual meal size with an increase in the number or frequency of meals [33], such that overall food intake is not altered. In rodents, exogenous administration of CCK also engages a complete behavioral satiety sequence, accompanied by periods of grooming and sleep [34]. Taken together, these observations clearly implicate CCK as a prototypical satiety signal, with meal-induced CCK secretion being a central event in the termination of individual meals.

The suppression of food intake by CCK is mediated primarily by the brain, although its effects on gastric emptying also contribute to its satiating effects. CCK receptors are expressed within multiple brain regions, and thus a direct effect of gut-derived CCK on the brain is one possible mechanism for CCK action. However, CCK receptors are also expressed on vagal afferents that project from the gut to the caudal brain stem. These vagal fibers are directly stimulated by CCK [35], and vagotomy significantly attenuates CCK-induced satiety index CCK-induced satiety [36]. The NTS is a key target for vagal sensory input, and exogenous CCK administration robustly activates c-Fos within NTS neurons [37, 38], as well as within other brain areas controlling food intake. In the brain stem, melanocortin neurons appear to be critical for the suppression of food intake by CCK, with activation of melanocortin-4 receptors (MC4R) required for the reduction of food intake [39]. These data therefore support a model in which CCK produced by the gut acts locally on vagal afferents, with these afferents then transmitting this satiety signal to key areas within the brain, and in particular the NTS. In summary, it is evident that CCK satisfies many of the requirements for a circulating satiety signal: it is produced by the gut in response to nutrient ingestion, suppresses meal size, acts rapidly but is short-lived, and does not induce illness or taste aversion. CCK consequently has become a prototypical satiety signal, and has provided a valuable benchmark by which to evaluate the many other proteins and gut hormones subsequently found to impact feeding behavior.

3.2. Peptide YY

Peptide YY (PYY), a member of the pancreatic polypeptide (PP) family which includes neuropeptide Y (NPY) and PP, is a 36-residue peptide with carboxy- and amino-terminal tyrosines (Y) that was isolated from porcine small intestine extracts in 1980 [40]. PYY is secreted from L cells of the gastrointestinal tract, with hydrolysis by the enzyme dipeptidyl peptidase-IV (DPP-IV) at the Pro²–Ile³ bond, producing PYY_{3–36} [41]. Full-length PYY_{1–36} is an agonist for at least three receptor subtypes (Y1, Y2, and Y5), with removal of the two amino terminus residues resulting in increased selectivity for the Y2 receptor [42, 43]. The Y2 receptor is widely expressed in the CNS, including the hypothalamus and brain stem. In the hypothalamus, Y2 mRNA is expressed on most NPY-positive neurons, with selective Y2 agonists acting to suppress the secretion of the potent orexigen NPY in hypothalamic slices [44]. Conversely, a selective Y2 antagonist stimulates NPY release, and also increases the release of an anorexigen, alpha-melanocyte stimulating hormone (α -MSH), in hypothalamic slices [44]. Overall, it has been proposed that the regulation of food intake by PYY_{3–36} involves the suppression of hypothalamic NPY/AgRP neurons, which are orexigenic, and stimulation of hypothalamic POMC/CART neurons, which are anorexigenic (Table 1). One group reported that mice lacking functional MC4R, which are the primary receptor involved in the regulation of food intake by α -MSH [45], do not respond to PYY_{3–36} [44, 46, 47]. However, a subsequent study reported that PYY_{3–36} reduced food intake in MC4R-deficient mice [48], while prohormone proopiomelanocortin (POMC) mice that lack α -MSH also respond to PYY_{3–36} [49], suggesting melanocortin-independent pathways for the regulation of feeding behavior by PYY_{3–36}.

The regulation of PYY secretion from the gut, and the regulation of the ratio of PYY_{1–36} to PYY_{3–36} in serum, by nutrient consumption, is consistent with this peptide acting as a satiety signal. PYY levels increase following a meal, peaking approximately 90 minutes after ingestion [50]. The ratio of PYY_{1–36} to PYY_{3–36} in human sera is also dependent on fed state, with PYY_{3–36} dominating postprandially [51]. Furthermore, in some experiments the administration of PYY_{3–36} reduces food intake in mice, and reduces meal size in humans [21, 44, 46, 48, 49].

It should be noted, however, that the role of PYY_{3–36} as a satiety signal has been the subject of controversy, with some groups having difficulty in demonstrating a significant suppression of food intake [20]. Moreover, PYY_{3–36} has also recently been reported to induce a vagal nerve dependent conditioned taste aversion, suggesting that the reduction of food intake in mice might be due to an illness-related behavioral response as opposed to a “satiety” signal [21].

3.3. Ghrelin

Ghrelin is distinguished from other gut peptides in that it is not a satiety factor, and is the first gut-secreted peptide described that, when infused chronically either intracerebroventricularly or peripherally, causes hyperphagia and weight gain. Two groups simultaneously reported the discovery of a transcript encoding a secreted peptide and expressed in the stomach. Kojima et al. identified a 28-residue protein while screening for ligands of the growth hormone secretagogue receptor (GHS-R), an orphan G-protein-coupled receptor. The full sequence encoding a 117-amino-acid protein was cloned from a rat stomach cDNA library, with the first 23 residues encoding a signal peptide and the 28-residue ghrelin sequence beginning at Gly24 [52]. Kojima et al. also reported that *O*-*n*-octanoylation of the peptide at Ser3 is essential for inducing a response of Chinese hamster ovary (CHO) cells expressing GHS-R. Given that the peptide is a potent GH secretagogue, Kojima et al. designated the peptide as “ghrelin,” based on the Proto-Indo-European root of the word “grow” [52].

Tomasetto et al. reported a transcript encoding a 117-amino-acid protein, identified in a screen for cDNAs expressed in the stomach [53]. This group designated the putative protein encoded by the transcript as motilin-related peptide (MRP), based on a weak homology with motilin, a peptide hormone that regulates smooth muscle contraction in the gastrointestinal tract. Tomasetto et al. were unable to show a biologic effect, owing to the use of a non-*O*-*n*-octanoylated, and hence biologically inactive peptide. Using Northern blot analysis, both groups demonstrated that ghrelin mRNA expression is highest in stomach, in enteroendocrine cells, with lower levels observed in the duodenum [52, 53]. Ghrelin immunoreactivity and mRNA have been reported in the hypothalamus, suggesting a possible role as an orexigenic neuropeptide [47, 52]. However, analysis of ghrelin knockout mice, in which the coding sequence is replaced by a *LacZ* reporter gene, failed to identify significant ghrelin-specific immunoreactivity, or β -galactosidase staining, in the hypothalamus [54].

Several observations suggest that ghrelin, in addition to regulating GH secretion, might regulate metabolism. GHS-R mRNA expression had earlier been reported in the hypothalamus and brain stem, while the GH secretagogue GHRP-6 stimulates c-Fos mRNA expression in arcuate nucleus NPY neurons, suggesting stimulation of a potent orexigenic neuropeptide [55–57]. Peripherally administered ghrelin affects energy balance by dose-dependently stimulating food intake and weight gain in rats and mice [58, 59]. In mice, the stimulation of food intake by ghrelin is dependent on two orexigenic peptides expressed in the hypothalamus, NPY and agouti-related protein (AgRP) [60, 61].

In humans, ghrelin acutely increases meal size, and can attenuate loss of appetite associated with cancer [62–64]. Ghrelin levels in the circulation exhibit an ultradian rhythm that is also consistent with this peptide stimulating

food intake. In marked contrast to other gut peptides, whose secretion peaks postprandially, ghrelin levels in the circulation peak in anticipation of meal ingestion [65], and decline thereafter in correlation with caloric load [66]. These results suggest that ghrelin might function to initiate meals, or as a signal of negative energy balance. Ghrelin knockout mice do not, however, exhibit differences in total 24-hour food intake and have normal body weight [67].

3.4. Amylin

Amylin, or islet amyloid polypeptide (IAPP), is a 37-amino-acid peptide that was purified from islets of individuals with type 2 diabetics [68]. Amylin is cosecreted with insulin from pancreatic β -cells [69, 70]. Many studies have shown that amylin is a short-term satiety peptide. Amylin levels index amylin levels in the circulation increase postprandially while administration of the peptide, or analogues thereof, suppresses food intake in rodents and can cause weight loss when administered chronically (reviewed in [71–73]). In humans with type 2 diabetes, pramlintide, an amylin analogue, improves insulin sensitivity and causes weight loss, with a recent study suggesting that pramlintide enhances satiety and reduces food intake [74]. Amylin may therefore have a role in the treatment of obesity by reducing food intake. The regulation of feeding behavior by amylin involves both CNS and peripheral mechanisms [71–73]. Neurons in the area postrema, a circumventricular organ located in the brain stem, are required for the inhibition of food intake by amylin, while the hypothalamus also contains amylin binding activity. In the periphery, amylin may also affect food intake by inhibiting gastric emptying.

Several receptors that interact with amylin have been recently identified [75]. They commonly share the calcitonin receptor domain at their core and are associated with different receptor activity-modifying proteins (RAMPS) that differentially affect amylin binding [76]. The specific distribution of these receptors and the nature of their roles in transducing amylin's effects on energy balance remain to be elucidated.

3.5. Enterostatin

Enterostatin is a pentapeptide cleaved from the amino-terminus of pancreatic procolipase by trypsin. Proteolytic cleavage of enterostatin from procolipase activates colipase, a cofactor for pancreatic lipase, promoting fat digestion [77–79]. In rats, experiments examining the effects of peripheral or intracerebroventricular administration of enterostatin indicate that this peptide selectively inhibits fat consumption [78, 79]. Further, the postprandial increase in enterostatin levels in the circulation of rats following a meal correlates with dietary fat content [80]. Together, these observations indicate that enterostatin might function as a specific regulator of fat consumption. However, while

the levels of immunoreactivity for one isoform of enterostatin also increase in humans postprandially [81], in a phase II trial intravenous administration of enterostatin did not significantly affect meal size in humans [82].

The mechanisms and receptors involved in the regulation of feeding behavior by enterostatin are unclear. Crude binding studies using brain lysates indicate two binding sites, one of low affinity ($K_d = 170$ nM) and one of high affinity ($K_d = 0.5$ nM). The low-affinity site might be the F1-ATPase β -subunit, which binds enterostatin with an affinity of 150 nM [83]. The suppression of food intake, and stimulation of c-Fos immunoreactivity in the NTS and parabrachial, paraventricular, and supraoptic nuclei in the brain is inhibited by vagotomy, suggesting that enterostatin interacts with the vagal system to regulate feeding behavior [84].

3.6. Glucagon-like Peptide

Glucagon-like peptide (GLP-1) is an intestinal peptide released by specialized endocrine cells in the gut (K-cells) in response to the ingestion of glucose or lipids [88]. GLP-1 is produced by the posttranslational processing of proglucagon (Figure 1), which contains several proglucagon-derived peptides (PGDP) [85]. GLP-1 suppresses food intake by acting peripherally to inhibit gastric emptying, and also acting centrally to reduce food intake in the short term, but not long term [88]. Centrally administered GLP-1 elicits a conditioned aversion, while GLP-1R antagonists inhibit the aversive response to the toxin lithium chloride [22–24]. GLP-1 may thus function as a satiety factor, but also appears to be involved in mediating the behavioral and stress response to visceral illness.

Exenatide, or exendin-4, is a GLP-1 synthetic mimetic that stimulates the release of insulin from pancreatic beta cells. Diabetic subjects treated with exenatide showed significantly improved diabetic status and weight loss, with minimal gastrointestinal distress [86], and has recently been approved by the FDA as adjunctive therapy for patients with type 2 diabetes marketed as the drug Byetta (Amylin/Lilly). GLP-1 mimetics such as exenatide may be better tolerated and therefore more useful as therapies for diabetes or energy balance disorders.

3.7. Bombesin Family: Bombesin, Gastrin-releasing Peptide and Neuromedin B

Bombesin was initially isolated from amphibian skin [87], and is expressed mainly in the brain and gastrointestinal tract. The two most well characterized mammalian homologues of bombesin, gastrin-releasing peptide (GRP) and neuromedin B (NMB), are also expressed in gut and brain, and can inhibit food intake when systemically administered in a number of mammalian

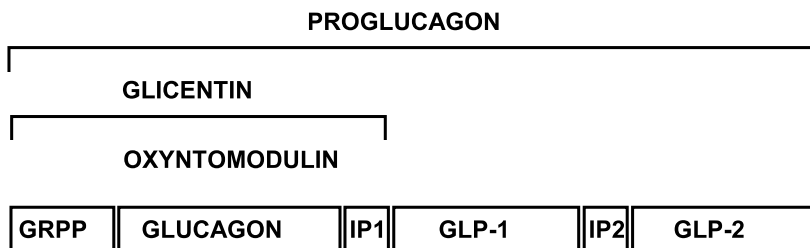


Figure 1. Structure of proglucagon, and a description of the proglucagon-derived peptides (PDRP) [85].

species, including humans [88, 89]. The effects of GRP and NMB are mediated through their respective receptors, GRP-R and NMB-R, although both peptides can bind both receptors. GRP-R is expressed throughout the brain including the hypothalamus whereas NMB-R is expressed in a more restricted fashion, particularly in the olfactory and thalamic areas [90]. More recently another receptor showing homology to GRP-R and NMB-R was cloned and designated bombesin-like peptide receptor subtype-3 (BRS-3) [91]. Expression of BRS-3 was limited to the hypothalamus and hindbrain. Both GRP and NMB have poor binding affinity for BRS-3, suggesting that the endogenous ligand for this receptor remains to be found. Mice deficient for either GRP-R or NMB-R exhibit no differences in food consumption and body weight compared to wild-type mice [92–94], although GRP-R may mediate some of the food intake inhibiting effects of bombesin and GRP [95]. BRS-3 knockout mice, however, are mildly obese, glucose intolerant, and leptin and insulin resistant [96], suggesting that BRS-3 may be a more important member of the hypothalamic appetite-regulatory network.

3.8. Oxyntomodulin

Oxyntomodulin, like GLP-1, is derived from enzymatic processing of the proglucagon gene (Figure 1), and is released from the small intestine after ingestion of food. Oxyntomodulin is a satiety signal and inhibits food intake in rodents when administered either centrally or peripherally [97], and has also been shown to have anorectic effects when given to human subjects [98], as well as to promote weight loss [99]. Oxyntomodulin treatment in humans reduces plasma ghrelin [98] and leptin levels, while increasing circulating levels of adiponectin [99]. The fact that oxyntomodulin interacts with the GLP-1R, albeit with significantly less affinity than GLP-1, suggest that its effects may be mediated by this receptor, although the existence of an oxyntomodulin-specific receptor remains a possibility.

3.9. Leptin

Leptin, encoded by the *ob* gene, is thought to be one of the most important hormones involved in energy homeostasis. Primarily secreted by adipocytes in response to positive energy balance, it circulates to areas of the brain, particularly the hypothalamus, and induces negative feedback responses. The wide range of functions and mode of action of leptin are described in more detail later. Leptin, however, is also produced in the stomach in response to feeding, as well as CCK treatment [100]. When leptin is administered via the celiac artery, which perfuses the upper gastrointestinal tract, it dose-dependently reduces meal size in normal, but not in vagotomized, rats [101]. In addition, leptin has also been shown to enhance the food-reducing effects of bombesin as well as CCK [101, 102]. The role of leptin in the modulation of gut-acting satiety peptides remains to be thoroughly understood.

4. NEUROENDOCRINE INDICATORS OF LONG-TERM ENERGY BALANCE: LEPTIN AND INSULIN

Abnormal metabolism of adipose tissue appears to be an important factor in the development of insulin resistance [103]. Increased adipose mass, and in particular abdominal obesity, increases risk for developing insulin resistance and associated comorbidities, such as cardiovascular disease. On the other hand, insufficient capacity or a failure of adipocytes to proliferate and store excess calories has been suggested to cause excess accumulation of TAG and fatty acids in tissues such as the liver and skeletal muscle, leading to insulin resistance [104]. Abnormal secretion and/or function of the adipokine leptin from adipose tissue is an important factor in the etiology of insulin resistance [103]. In relation to the neuroendocrine control of food intake, leptin is considered one of, if not the, primary neuroendocrine signal of long-term energy balance [105]. Loss of function mutations in the leptin (*Lep*) or leptin receptor (*Lepr*) genes are associated with severe obesity and hyperphagia in mice and in a small number of humans who are homozygous for *Lep* or *Lepr* mutations [106]. Leptin resistance could therefore be an important factor in disorders of energy intake and expenditure causing obesity and insulin resistance [105]. This hypothesis is supported by the observation that the inactivation of genes that inhibit LEPR signal transduction in mice is associated with increased leptin sensitivity, and protection from the development of obesity and leptin resistance in obesogenic environments [107, 108].

In both humans and animals, physiological mechanisms monitor body adipose mass and react to changes in energy balance by altering ingestive behavior and energy expenditure to buffer against drastic changes in body adi-

posity and restore body weight and adiposity once the nutritional challenge dissipates [109–111]. This process of maintaining a relatively constant level of energy stores over time is known as energy homeostasis, and neuronal circuits within the brain, and in particular the hypothalamus, are critically involved in this process [109–111]. These circuits are sensitive to changes in a variety of circulating nutritional cues, and two hormones that are critical for the homeostatic regulation of body weight are the adiposity signals insulin and leptin.

In 1953, Kennedy first articulated the hypothesis that circulating signals produced by or in proportion to adipose mass act within the brain to reduce food intake [112]. These signals would decrease in response to reductions in body adiposity and conversely increase as body fat mass increases, and would thus represent a negative feedback signal for adiposity. The brain would then “sense” changes in these adiposity signals and regulate food intake and energy expenditure to normalize body adiposity. This initial hypothesis for a functional adipostat was supported by Coleman, who extended this hypothesis by demonstrating that the mouse obesity mutations *ob* (obese, now *Lep^{ob}*) and *db* (diabetic, now *Lepr^{db}*) represented mutations in what was likely a circulating cue and its corresponding receptor, such that the lack of either this putative hormone or its receptor resulted in massive obesity [113]. In 1994 Zhang and colleagues first cloned the obesity (*ob*) gene [114], and it was soon demonstrated that its protein product leptin was indeed a circulating hormone that acted within the brain to suppress feeding [115–122]. Leptin satisfies many of the requirements of an adiposity signal, being produced and secreted by adipocytes via mechanisms that are sensitive to both the chronic level of body adipose mass as well as current metabolic status. Circulating leptin levels increase in response to increases in adipose mass and glucose flux into adipocytes, while levels rapidly fall during periods of negative energy balance. Thus circulating leptin levels are a relatively accurate marker of the nutritional and metabolic status of the organism. While leptin does have clear effects on peripheral tissues, its profound effects on feeding and energy homeostasis are primarily mediated by the brain, where leptin acts to suppress food intake; stimulate energy expenditure; and also influence reproduction, glucose homeostasis, and a number of additional physiological systems. In addition, leptin or leptin receptor deficiency in both humans and animal models results in a profound obesity phenotype, marked by hyperphagia, diabetes, and infertility. Thus appropriate leptin signaling within the brain is necessary for energy homeostasis, and this work collectively supports the role of leptin as an adipostatic signal to the brain.

Other neuroendocrine signals also appear to satisfy the criteria of an adiposity signal. Much of the work focusing on leptin as an adiposity signal was preceded by a series of studies suggesting that insulin functions as an adiposity